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THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

Sponsor: US Army Medical Materiel Development Activity

Test Article: Halofantrine HCl

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Study Director

Barry S. Levine, D.Sc., D.A.B.T.

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This study evaluated the toxicity of halofantrine hydrochloride in B6C3F1 mice following thirteen weeks of daily oral (gavage) administration. Halofantrine HCl is being developed by WRAIR as an oral antimalarial treatment. Dose levels studied were 0 (vehicle control), 1, 5 and 25 mg/kg/day, and were based on a four week dose range-finding test in which mortality occurred at 100 mg/kg/day with anemia present at 20 and to a minimal extent at 4 mg/kg/day. The drug or vehicle was administered to 10 mice/sex/group. The animals were ≈ 8 weeks old and weighed 23.0 - 25.8 g (males) and 17.7 - 21.7 g (females) at treatment initiation.

No clinical signs of toxicity were observed and body weight gains and food consumption were not affected by test article treatment. Treatment-related ophthalmic changes were also not observed. The primary treatment-related effects of halofantrine were microcytic anemia and marginal changes in the liver. An increased severity and/or incidence of hepatic glycogen depletion was observed in high dose animals compared to control mice. In addition, individual cell necrosis was seen in two high dose females but not males. These marginal liver changes were accompanied by statistically insignificant increased serum ALT levels and decreased total protein and albumin levels in high dose males. Marginal treatment-related anemia, including decreases in hemoglobin, hematocrit, mean corpuscular volume (MCV) and/or mean corpuscular hemoglobin (MCH), in the absence of a reduction in RBC count, was observed in high dose animals. These microcytic anemic changes without corresponding compensatory responses or histopathologic changes in bone marrow are suggestive of an iron-deficiency anemia. Very slight but statistically significant microcytosis was also seen in mid dose males, but was not considered biologically significant.

The no-observed effect level (NOEL) in the present study was considered to be at or near 5 mg/kg/day. This study was conducted to select dose levels for a subsequent two year carcinogenicity study in mice. Because marginal halofantrine-induced toxicity including anemia and mild liver toxicity was seen in high dose animals (25 mg/kg/day), the following dose level ranges are suggested: 2 - 4 , 7 - 12 and 25 - 35 mg/kg/day. Accordingly, dose levels of 3, 10 and 30 mg/kg/day are recommended.

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STATEMENT OF COMPLIANCE

Study No. 166 entitled "Three Month Oral (Gavage) Toxicity Study of Halofantrine Hydrochloride in Mice" was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects.

The protocol for this study was approved by the UIC Animal Care Committee.

Signature

Study Director

_____ _____

Barry S. Levine, D.Sc., D.A.B.T. Date

QUALITY ASSURANCE STATEMENT

STUDY TITLE: THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

STUDY NUMBER: 166

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 8/26/94

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance personnel monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

The following are the inspection dates, phases inspected, and report dates of QA inspections of the study.

INSPECT ON 8/26/94, TO STUDY DIR 8/26/94, TO MGMT 8/26/94
PHASES: PROTOCOL REVIEW

INSPECT ON 2/13/95, TO STUDY DIR 2/14/95, TO MGMT 2/15/95
PHASES: BODY WEIGHT AND ACCLIMATIZATION TO ORAL DOSING

INSPECT ON 2/14/95, TO STUDY DIR 2/15/95, TO MGMT 2/16/95
PHASES: TEST ARTICLE PREPARATION, EAR TAGGING AND IMPLANTATION OF MICRO-CHIP IDENTIFICATION DEVICE

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PHASES: OPHTHALMIC EXAMINATION

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PHASES: RAW DATA AND DRAFT REPORT FROM THE ANALYTICAL LABORATORY

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THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

Test Article.: Halofantrine HCl (WR171669)

Sponsor: US Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5009

Sponsor Representative: George J. Schieferstein, Ph.D.

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
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Barry S. Levine, D.Sc., D.A.B.T. Date
Study Director

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Clyde W. Wheeler, PhD. Date
Toxicologist

Study Initiation: August 26, 1994
Dosing Initiation: February 16, 1995
In-Life Completion: May 19, 1995

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1. SUMMARY

This study evaluated the toxicity of halofantrine hydrochloride in B6C3F1 mice following thirteen weeks of daily oral (gavage) administration. Halofantrine HCl is being developed by WRAIR as an oral antimalarial treatment. Dose levels studied were 0 (vehicle control), 1, 5 and 25 mg/kg/day, and were based on a four week dose range-finding test in which mortality occurred at 100 mg/kg/day with anemia present at 20 mg/kg/day and to a minimal extent at 4 mg/kg/day. The drug or vehicle was administered to 10 mice/sex/group. The animals were ≈ 8 weeks old and weighed 23.0 - 25.8 g (males) and 17.7 - 21.7 g (females) at treatment initiation.

The study results are summarized in Table 1. No clinical signs of toxicity were observed and body weight gains and food consumption were not affected by test article treatment. Treatment-related ophthalmic changes were also not observed. The primary treatment-related effects of halofantrine were microcytic anemia and marginal changes in the liver. An increased severity and/or incidence of hepatic glycogen depletion was observed in high dose animals compared to control mice. In addition, individual cell necrosis was seen in two high dose females but not males. These marginal liver changes were accompanied by statistically insignificant increased serum ALT levels and decreased total protein and albumin levels in high dose males. Marginal treatment-related anemia, including decreases in hemoglobin, hematocrit, mean corpuscular volume (MCV) and/or mean corpuscular hemoglobin (MCH), in the absence of a reduction in RBC count, was observed in high dose animals. These microcytic anemic changes without corresponding compensatory responses or histopathologic changes in bone marrow are suggestive of an iron-deficiency anemia. Very slight but statistically significant microcytosis was also seen in mid dose males, but was not considered biologically significant.

The no-observed effect level (NOEL) in the present study was considered to be at or near 5 mg/kg/day. This study was conducted to select dose levels for a subsequent two year carcinogenicity study in mice. Because marginal halofantrine-induced toxicity including anemia and mild liver toxicity was seen in high dose animals (25 mg/kg/day), the following dose level ranges are suggested: 2 - 4 , 7 - 12 and 25 - 35 mg/kg/day. Accordingly, dose levels of 3, 10 and 30 mg/kg/day are recommended.

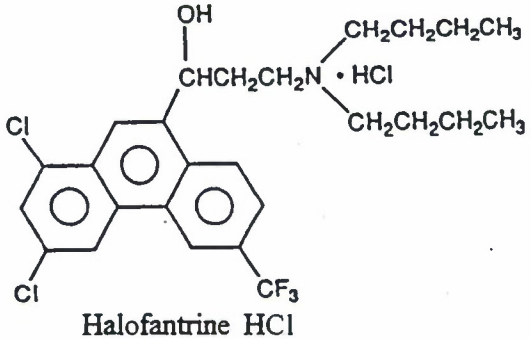
2. INTRODUCTION

This study was conducted to determine the specific target organ toxicity, dose-response relationships and determination of a no-adverse effect level of Halofantrine HCl in mice following thirteen weeks of daily oral administration. Halofantrine HCl is being developed by WRAIR as an oral antimalarial treatment. The study design was based on the 1993 OECD Guidelines for Testing of Chemicals; Subchronic Oral Toxicity - Rodent: 90- day study. The results of this study will be used to select dose levels for a subsequent two year oral carcinogenicity study of halofantrine HCl in mice. The study was conducted in accordance with the specifications of the Sponsor. The B6C3F1 mice used in the study are a standard and accepted rodent species for regulatory toxicology studies, and were specified by the Sponsor. Oral administration is the intended clinical route and was also specified by the Sponsor. All methods and procedures were conducted in accordance with the Quality Assurance Programs of the Toxicology Research Laboratory, University of Illinois at Chicago and Pathology Associates, Inc., designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. Dosing was initiated on February 16, 1995 and the in-life portion was terminated on May 19, 1995.

3. MATERIALS AND METHODS

3.1 Test Article

Halofantrine HCl (WR171669), Bottle No. BM01792, a white powder, was provided by the Sponsor. It was received on September 20, 1994 from Herner & Co., and was assigned an in-house chemical number (1950614). It was stored at ambient temperature and humidity. The Certificate of Analysis accompanying the test article indicated that the purity was 100% (analysis performed at Laboratorious Julian de Mexico, Smithkline Beckman Co.). The chemical structure of halofantrine HCl is shown below.



Halofantrine HCl

The Analytical Chemistry Report is contained in Appendix 1. The test article was initially identified by Nuclear Magnetic Resonance (NMR) spectroscopy and the purity was determined to be 100%; no contaminating purities were detected. The purity was re-determined following the completion of the in-life portion of the study. At that time, the purity was also determined to be 100%. Thus, the test article was stable under storage conditions.

3.2 Animals

Fifty male and 50 female B6C3F1 Virus Antibody Free (VAF) mice were obtained from Charles River Breeding Laboratories (Portage, MI) on February 8, 1995. The animals were approximately 7 weeks old upon arrival at the UIC AAALAC-accredited animal facility (date of birth December 27, 1994). Each animal was given a study-unique quarantine/pretest number following placement in cages. The animals were singly housed in polycarbonate cages with Anderson bed-o-cob bedding (Heinhold, Kankakee, IL) in a temperature (65 - 78°F) and humidity (30 - 70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 395 cm^2 and 12.5 cm height, was adequate to house mice at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHEW (NIH) No. 86.23. All animals were routinely transferred to clean cages once weekly.

Certified Rodent Chow No. 5002 (PMI Feeds Inc., St. Louis, MO) was provided *ad libitum* from arrival until termination. Tap water from an automatic watering system in which the room distribution lines were flushed daily was provided *ad libitum*. The water was not treated with additional chlorine or HCl. There were no known contaminants in the feed or water which were expected to influence the study. The results of the bimonthly comprehensive chemical analyses of Chicago water performed by the City of Chicago are documented in files maintained by Quality Assurance.

3.3 Experimental Design

All animals were examined daily during the eight day quarantine/pretest period, and were approved for use by the Clinical Veterinarian prior to being placed on test. Near the end of the quarantine/pretest period, 40 animals of each sex were randomized by sex into the groups shown in the following table using a computer-generated randomization program, stratified on the basis of body weight.

Treatment Group	Dose Level (mg/kg/day)	Number of Males	Number of Females
1	0	10	10
2	1	10	10
3	5	10	10
4	25	10	10

Dose levels were selected on the basis of a previously conducted 4 week oral dose range-finding study in mice (UIC/TRL Study No. 168) and following discussions with the Sponsor. The number of animals/sex/group was necessary for adequate statistical analysis.

During the test animal selection process, each animal was assigned an animal number unique to it within the population making up the study. This number appeared as an ear tag and was also coded on a subcutaneously implanted microchip. It also appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, sex, treatment group number and dose level. Cage cards were color-coded as a function of treatment group.

Dosage formulations were prepared once weekly and were administered daily by gavage, at a dosing volume of 10 ml/kg/day, 7 days a week. Suspensions were prepared on the basis of the weight of the hydrochloride salt of halofantrine. The 0.5% methylcellulose vehicle was prepared at least weekly by placing the required amount of deionized water in a beaker and then adding the required amount of methylcellulose which was weighed on an analytical balance (0.5 g of methylcellulose per 100 ml of deionized water). The mixture was stirred until homogeneous and then refrigerated. One lot of methylcellulose (Sigma Chemical Co., Lot No. 123H0589) was used in this 3 month toxicity study and in the previously conducted 4 week dose range-finding study (UIC/TRL Study No. 168).

For the first study week, a stock test article dosing suspension, which was also the high dose formulation, was prepared by triturating the appropriate amount of halofantrine HCl with approximately one-third to one-half of the required 0.5% methylcellulose vehicle in a mortar. The mixture was transferred to a graduated cylinder, the mortar was rinsed with vehicle and added to the graduated cylinder, and the final volume was brought to mark with vehicle. The entire mixture was then thoroughly stirred. The mid and low dose level suspensions were prepared by diluting and thoroughly mixing an appropriate volume of the high dose formulation with additional vehicle.

During subsequent study weeks, each test article dosing suspension was prepared individually by adding the appropriate amount of halofantrine HCl with the required volume of vehicle in a pre-calibrated beaker. The contents was mixed with an Omni-

Mixer homogenizer for at least 5 minutes. All suspensions were stored at 2 - 8°C. All suspensions were allowed to warm to room temperature and stirred continuously before and during gavage administration. Samples of all dosing suspensions (including controls) prepared at the onset of weeks 1, 3, 7, 10 and 13 were analyzed prior to use, and only suspensions within 10% of their target concentration were used. In addition, approximately 10 ml aliquots from each weekly dosing suspension set were retained and frozen at -20°C for possible analysis.

The test article was administered by gavage once daily for 91 or 92 days commencing on February 16, 1995 (day 0). Control animals received the test article vehicle. All animals received the vehicle by gavage on days -3 to -1 to acclimate them to the procedure. All animals were dosed up to and including the day prior to their scheduled necropsy. Dosing volume was 10 ml/kg/day, adjusted on the basis of each animal's most recent body weight. The actual volume (ml) administered was documented in the raw data. The mice weighed 23.0 - 25.8 g (males) and 17.7 - 21.7 g (females) on day 0 and were approximately eight weeks old at initiation of treatment.

Non-fasted body weights were recorded on day -3, on day 0, weekly thereafter and at scheduled termination. Clinical signs were observed and recorded for all animals once daily, approximately 1 - 2 hours after dosing. The general behavior, posture, locomotion, breathing pattern and coat were observed for all animals. The animals were also observed immediately prior to dosing and in the afternoon for moribundity/mortality. Physical examinations (clinical observations) which included examination of eyes and all orifices were conducted once weekly commencing in week -1. Food consumption was measured for all animals weekly commencing with week -1. All mice were examined by indirect ophthalmoscopy prior to study initiation (Week -1) and during Week 13. The animals were treated with 1% atropine sulfate eye drops prior to the examination.

Hematology and clinical chemistry parameters were measured in all surviving animals at necropsy (days 91/92). Hematology parameters were measured in one-half the animals (5 animals/sex/group) and clinical chemistry parameters were measured in the remaining animals (5 animals/sex/group). For the "hematology" animals, blood for serum harvest was also collected. This serum was used to complete the battery of clinical chemistry tests. The non-fasted animals were anesthetized by carbon dioxide inhalation (70% CO_2:30% O_2), and approximately 0.5 - 0.75 ml of blood were collected from the orbital sinus to measure the following parameters. Additionally, blood was also obtained via intracardial puncture for clinical chemistry determinations from several animals (animal nos. 223, 224, 230, 246, 247, 261, 263, 268 and 269). The samples were processed in the same random order as collected.

Hematology

[a]Erythrocyte count and morphology
Hematocrit
Hemoglobin
Leukocyte count, total and differential
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Platelet count
Reticulocyte count

[a] Includes nucleated RBCs.

Clinical Chemistry

The clinical chemistry tests were prioritized as shown on the basis of the sample volume obtained.

(1) Thyroid stimulating hormone (TSH)[a]
(2) Alanine aminotransferase (ALT)
(3) Alkaline phosphatase
(4) Cholesterol
(5) Glucose
(6) BUN
(7) Triglycerides
(8) Sorbitol dehydrogenase (SDH)
(9) Total protein
(10) Albumin (A)
(11) Globulin (G) (calc.)
(12) A/G ratio (calc.)
(13) Total bile acids
(14) Inorganic phosphorus

[a]Serum were frozen at -70°C and shipped to Anilytics Incorporated (Gaithersburg, MD) for the measurement of TSH levels. The analysis was performed under GLP regulations.

All animals were sacrificed and necropsied in random order following thirteen weeks of treatment over a two consecutive day period (days 91 or 92). Euthanasia was accomplished by carbon dioxide asphyxiation (70% CO_2:30% O_2), and an extensive necropsy was performed under the direction and supervision of the pathologist. Terminal body weights were collected prior to routine sacrifice. The necropsy procedure was a thorough and systematic examination and dissection of the animal viscera and carcass, and collection and fixation of the following tissues/organs in 10% neutral buffered formalin. The ear with its attached identification tag and the subcutaneously implanted microchip were saved with the wet tissues.

Adrenal glands
*Brain
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes with harderian glands
Femur with marrow
Gallbladder
Gross lesions
*Heart
Ileum
Jejunum
*Kidneys
*Liver
*Lungs/Bronchi
Lymph node (mesenteric)
Ovaries
Pancreas
Pituitary
Prostate
Salivary gland (submaxillary)
Sciatic nerve
Skeletal muscle
Skin (abdominal) with mammary gland
Spinal cord (thoracic)
*Spleen
Stomach
*Testes
Thymus
Thyroid gland/Parathyroids
Tongue
Trachea
Ureter
Urinary bladder
Uterus
Vagina

*Weighed at scheduled necropsy. Paired organs were weighed as a unit.

All tissues and organs collected at necropsy were examined microscopically in all control and high dose animals. If treatment-related lesions were observed at the high dose, those tissues/organs were examined microscopically within sex in mid and low dose animals. Gross lesions were examined microscopically in all animals.

3.4 Statistical Analyses

For each sex, Analysis of Variance tests were conducted on body weight, weight gains, food consumption, hematology, clinical chemistry and organ weight data. Organ weight analysis considered weights relative to brain weight. If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's t test was used for pair-wise comparisons to the control group. In addition to the written report, individual data in "ASCII" form and summary data tables of parameters and variability were transmitted to the Sponsor on magnetic media (computer diskette).

4. RESULTS

4.1 Dosage Formulation Analyses

The Analytical Chemistry Report is contained in Appendix 1. Dosage formulation analyses are shown in Table 2.

All dosing suspensions which were tested prior to use on the first day of weeks 1, 3, 7, 10 and 13 were within 10% of their target concentrations.

4.2 Mortality and Clinical Signs

Summaries of clinical signs are presented in Tables 3.1 - 3.2. Individual clinical signs and the daily incidence of clinical signs are contained in Appendix 3.

No animals died during the study and treatment-related clinical signs were not observed.

4.3 Body Weight

Summaries of body weights and weight gains are presented in Tables 4.1 - 4.2 and 5.1 - 5.2, respectively. Individual body weights and weight gains are contained in Appendix 4. In addition, summaries of body weights are graphically depicted in Figures 1 (males) and 2 (females).

Treatment-related changes in body weight and body weight gains were not seen. Sporadic fluctuations in weekly body weight gains were seen in high dose males in the fourth week of treatment and in high dose females during the second and third weeks of treatment. These changes were not considered biologically significant.

4.4 Food Consumption

Summaries of food consumption are presented in Tables 6.1 - 6.2. Individual food consumption (period data and calculated daily intake data) are shown in Appendix 5.

Food intake was not affected by test article treatment in males or females. However, on several occasions (weekly periods ending on days 14, 21, 63 and 84) apparent, nondose-

related decreases in food intake were seen in test article-treated female groups. These apparent reductions resulted from artificially high food intake values in control females during these periods and not due to decreased food consumption in test article groups. Although the reasons for this increase in control females is not known, spillage may have been a factor. A nondrug-related effect is supported by a lack of test article treatment on body weight (Section 4.3).

4.5 Clinical Pathology

Summaries of clinical chemistry tests are presented in Tables 7.1 - 7.2. Individual clinical chemistry data are in Appendix 6. Summaries of hematology tests are presented in Tables 8.1 - 8.2. Summaries of MCV and MCH data are also graphically depicted in Figures 5 and 6, respectively. Individual hematology data are in Appendix 8.

Although not statistically significant (possibly due to intra-animal variability), marginal increases in serum ALT levels in high dose animals and decreases in total protein and albumin levels in high dose males were seen. In addition, thyroid stimulating hormone (TSH) levels were slightly increased in mid and high dose males compared to control males, but again were not statistically significant possibly due to intra-animal variability. TSH levels were not affected in test article-treated females or in low dose males.

Minimal, but significant dose-related changes in RBC parameters were observed in high dose males and females. Decreases in hemoglobin, hematocrit, mean corpuscular volume (MCV) and/or mean corpuscular hemoglobin (MCH) of ≈ 7 - 9% were seen in high dose animals, although RBC counts were not significantly reduced (Figures 3 - 6). A very slight, but statistically significant decrease in MCV (≈ 2%) was also seen in mid dose males, but was not associated with other RBC changes (Figure 5). Although it was apparently treatment-related, microcytosis in mid dose males was not considered biologically significant.

No other clinical pathology changes were considered to be related to halofantrine HCl treatment.

4.6 Ophthalmology

The Ophthalmology Report is contained in Appendix 9.

No test article-related ophthalmic lesions were observed during the study.

4.7 Organ Weights

Organ weight summaries expressed as % brain weight are presented in Table 9.1 and 9.2. Individual organ weight data are contained in Appendix 10.

At necropsy (days 91 - 92), no treatment-related changes were seen in organ weights.

4.8 Pathology

The Pathology Report is contained in Appendix 11. A summary of microscopic lesions is shown in Table 10.

The oral administration of halofantrine HCl in mice was associated with microscopic

changes in the liver. A greater severity and/or incidence of glycogen depletion was seen in the liver in high dose animals [10 out of 10 males (severity =1.9) and 8 out of 10 females (severity = 1.3)] compared to control animals [8 out of 10 males (severity = 1.0) and 2 out of 10 females (severity = 0.2)]. This change was characterized by hepatocytes which lacked a coarsely vacuolated cytoplasm and had a more deeply and uniformly eosinophilic cytoplasm. Glycogen depletion was confined to the centrilobular regions in minimally affected animals, but the entire lobule was involved in the liver of animals having moderate glycogen depletion. An increase in severity compared to control animals was not seen in low and mid dose animals.

Minimal individual cell necrosis consisting of the presence of small foci of cellular debris in hepatic parenchyma in the periportal region was observed in the liver in two high dose females. This change was not seen in high dose males or in lower dose groups.

No other microscopic changes were considered to be related to halofantrine HCl treatment. A small meningioma in the brain was seen in one high dose female (animal no. 279), but was considered to be an incidental finding.

5. DISCUSSION/CONCLUSION

This study evaluated the toxicity of halofantrine HCl in B6C3F1 mice following thirteen weeks of daily oral (gavage) administration. The results are summarized in Table 1. No clinical signs of toxicity were observed, nor were body weights and food consumption affected by test article treatment. Treatment-related ophthalmic changes were not observed.

Microscopic changes were seen in the liver in high dose animals. This included glycogen depletion (incidence and/or severity greater than corresponding control animals), and individual cell necrosis in 2 of 10 high dose females. These minimal to mild changes were accompanied by nonstatistically significant increases in serum ALT levels (both sexes) and decreases in total protein and albumin levels in high dose males but not females. Glycogen depletion was observed in the absence of decreased food intake, suggesting that this was a direct biochemical effect of treatment. Taken together, this suggests that halofantrine HCl may be marginally hepatotoxic at 25 mg/kg/day.

Minimal, treatment-related anemia was observed in high dose animals. After thirteen weeks of treatment, decreases in hemoglobin, hematocrit, mean corpuscular volume (MCV) and/or mean corpuscular hemoglobin (MCH) were seen in high dose animals. Biologically significant changes in RBC parameters were not apparent in lower dose groups. These microcytic, anemic changes without corresponding compensatory responses or histopathologic changes in bone marrow are suggestive of an iron-deficiency anemia (Jain, 1986).

In the previously conducted dose range-finding four week oral toxicity study of halofantrine in mice (UIC/TRL Study No. 168), the dose levels were 4, 20 and 100 mg/kg/day. Frank test article-induced toxicity was seen in high dose animals and included the early death of five of five high dose males. Clinical signs of toxicity (rough coat, hunched posture, decreased activity and lethargy) and decreased body weight gains were seen in high dose animals. Splenic lymphocytic necrosis, observed in high animals, and moderate splenic lymphocytic depletion, were considered possible contributing factors to the deaths of the high dose males. Splenic granulopoiesis secondary to the splenic lymphocytic necrosis, supported by neutrophilia and splenomegaly, was observed in high dose females. Marginal leukopenia, consisting of decreased numbers of mature neutrophils and lymphocytes, was seen in mid dose males but not females and may be indicative of the initial insult producing splenic lymphocytic depletion in the high dose animals. Dose-

related, mild, microcytic, apparent iron-deficiency anemia was seen in high dose females and to a lesser extent in mid dose animals and low dose females. Thrombocytosis in high dose females may have been secondary to the anemia. Increased serum ALT and cholesterol levels in high dose females and increased serum ALT in mid dose males, not accompanied by corresponding histologic changes, suggests that halofantrine may be marginally hepatotoxic, as was seen in the current study.

The no-observed effect level (NOEL) in the present study was considered to be at or near 5 mg/kg/day. This study was conducted to select dose levels for a subsequent two year carcinogenicity study in mice. Because marginal halofantrine-induced toxicity including anemia and possible liver toxicity was seen in high dose animals (25 mg/kg/day), in addition to the results of the above-referenced four week dose range-finding test, the following dose level ranges are suggested: 2 - 4 , 7 - 12 and 25 - 35 mg/kg/day. Accordingly, doses of 3, 10 and 30 mg/kg/day are recommended.

6. REFERENCES

Jain, N.M. (1986). Blood loss or hemorrhagic anemias. In *Schalm's Veterinary Hematology*. Lea & Febiger, Philadelphia, p. 581.

7. PERSONNEL

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
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Report preparation was assisted by Mr. Mukesh Pitroda, B.S.

8. ARCHIVES

The raw data, specimens, test article reserves, and final report are archived at the Toxicology Research Laboratory (TRL), University of Illinois at Chicago (UIC), Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612-7353.

DRAFT

Table 1

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Summary of Toxic Responses

Dose (mg/kg/day)	0	•	•	25
Mice/Sex	10	NE	10	10
Deaths	0	0	0	0
Clinical Signs	-	NE	NE	NE
Body Weights/Gains	-	NE	NE	NE
Food Consumption	-	NE	NE	NE
Clinical Chemistry	-	NE	NE	↑ ALT (M?) ↓ TP (M?) ↓ ALB (M?)
Hematology	-	NE	NE	↓ HGB (M) (F?) ↓ HCT ↓ MCV ↓ MCH (M)
Organ Weights (% brain weight)	-	NE	NE	NE
Histopathology	LIVER - Glycogen depletion [8M(1.0)/2F(0.2)][a]	LIVER - Glycogen depletion [8M(0.9)/2F(0.2)][a]	LIVER - Glycogen depletion [10M(1.9)/1F(0.1)][a]	LIVER - Glycogen depletion [10M(1.9)/8F(1.3)][a] - Necrosis (2F)

CONCLUSIONS

The primary treatment-related effects of halofantrine were marginal changes seen in the liver and in RBC formation. No clinical signs of toxicity were observed and body weight gains and food consumption were not affected by test article treatment. Treatment-related ophthalmic changes were also not observed. An increased severity and/or incidence of hepatic glycogen deletion was observed in high dose animals compared to control animals. In addition, individual cell necrosis was seen in 2 of 10 high dose females but not males. These marginal liver changes were accompanied by statistically insignificant increased serum ALT levels (both sexes) and decreased total protein and albumin levels in high dose males. Marginal treatment-related anemia, including decreases in hemoglobin, hematocrit, mean corpuscular volume (MCV) and/or mean corpuscular hemoglobin (MCH), was observed in high dose animals. These microcytic anemic changes without corresponding compensatory responses or histopathologic changes in bone marrow are suggestive of an iron-deficiency anemia. The no-observed effect level (NOEL) in the present study was considered to be at or near 5 mg/kg/day. This study was conducted to select dose levels for a subsequent two year carcinogenicity study in mice. Because marginal halofantrine-induced toxicity including anemia and possible liver toxicity was seen in high dose animals (25 mg/kg/day), in addition to the results of a previously conducted dose range-finding test (UIC/TRL Study No. 168), the following dose level ranges are suggested: 2 - 4 , 7 - 12 and 25 - 35 mg/kg/day. Accordingly, doses at 3, 10 and 30 mg/kg/day are recommended.

ALT = alanine aminotransferase
TP = total protein
ALB = albumin
HGB = hemoglobin
HCT = hematocrit
MCV = mean corpuscular volume
MCH = mean corpuscular hemoglobin
[a]No. of animals (mean group severity)

? = Possible or marginal effect
NE = No effect
M = Male
F = Female

Table 2

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Dosage Formulation Analyses[a]

	Week 1		Week 3		Week 7	
Target Concentration (mg/ml)	Actual Concentration (mg/ml)	% Target	Actual Concentration (mg/ml)	% Target	Actual Concentration (mg/ml)	% Target
0	0.00	----	0.00	----	---	---
0.1	0.1036 ± 0.0008	103.6	0.1061 ± 0.0014	106.1	0.0997 ± 0.0006	99.7
0.5	0.5430 ± 0.0021	108.6	0.4894 ± 0.0029	97.9	0.5359 ± 0.0036	107.2
2.5	2.4146 ± 0.0303	96.6	2.5414 ± 0.0379	101.7	2.5798 ± 0.0166	103.2

	Week 10		Week 13	
Target Concentration (mg/ml)	Actual Concentration (mg/ml)	% Target	Actual Concentration (mg/ml)	% Target
0	0.00	---	0.00	----
0.1	0.1027 ± 0.0012	102.7	0.0956 ± 0.0012	95.6
0.5	0.5199 ± 0.0034	104.0	0.4822 ± 0.0048	96.4
2.5	2.5776 ± 0.0411	103.1	2.5136 ± 0.0529	100.5

[a]Mean ± standard deviation for triplicate runs.

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Table 3.1

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF CLINICAL SIGNS

STUDY: 166 SEX: MALE

DOSE: (mg/kg/day)	0	1	5	25
GROUP:	1-M	2-M	3-M	4-M
Scheduled Sacrifice	10	10	10	10
Normal	10	10	10	10
Total Number of Animals	10	10	10	10

Table 3.2

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF CLINICAL SIGNS

STUDY: 166 SEX: FEMALE

DOSE: (mg/kg/day)	0	1	5	25
GROUP:	1-F	2-F	3-F	4-F
Scheduled Sacrifice	10	10	10	10
Normal	10	10	10	10
Total Number of Animals	10	10	10	10

Table 4.1

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 166 SEX: MALE

PERIOD	DOSE: (mg/kg/day) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY -3	MEAN	23.6	23.7	23.7	23.6
	S.D.	0.60	0.76	0.61	0.77
	N	10	10	10	10
DAY 0	MEAN	24.7	24.2	24.5	24.5
	S.D.	0.52	0.78	0.54	0.99
	N	10	10	10	10
DAY 7	MEAN	26.1	25.4	25.7	25.4
	S.D.	0.56	0.69	1.04	0.93
	N	10	10	10	10
DAY 14	MEAN	26.9	26.7	26.7	26.4
	S.D.	0.89	0.92	0.92	1.09
	N	10	10	10	10
DAY 21	MEAN	27.0	26.5	26.7	26.5
	S.D.	0.89	0.82	1.14	1.04
	N	10	10	10	10
DAY 28	MEAN	27.7	27.0	27.2	26.9
	S.D.	1.07	0.72	1.10	1.00
	N	10	10	10	10
DAY 35	MEAN	28.0	27.4	27.7	27.4
	S.D.	1.00	0.91	1.29	1.21
	N	10	10	10	10
DAY 42	MEAN	28.6	28.0	28.3	27.9
	S.D.	0.98	0.70	1.41	1.30
	N	10	10	10	10
DAY 49	MEAN	28.9	28.3	28.3	28.3
	S.D.	0.96	0.67	1.10	1.27
	N	10	10	10	10
DAY 56	MEAN	28.9	28.7	28.8	28.6
	S.D.	0.96	0.78	1.32	1.30
	N	10	10	10	10

Analysis of Variance using DUNNETT'S Procedure

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 166 SEX: MALE

PERIOD	DOSE: (mg/kg/day) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 63	MEAN	29.4	28.8	29.2	28.8
	S.D.	1.51	0.89	1.63	1.28
	N	10	10	10	10
DAY 70	MEAN	29.7	29.4	29.5	29.2
	S.D.	1.48	1.14	1.60	1.40
	N	10	10	10	10
DAY 77	MEAN	29.9	29.9	30.0	29.3
	S.D.	1.44	1.02	2.16	1.46
	N	10	10	10	10
DAY 84	MEAN	30.1	30.2	30.0	29.7
	S.D.	1.65	0.92	1.88	1.44
	N	10	10	10	10
DAY 90	MEAN	30.0	30.3	30.3	29.8
	S.D.	1.48	1.00	1.78	1.59
	N	10	10	10	10

Analysis of Variance using DUNNETT'S Procedure

Table 4.2

DRAFT THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 166 SEX: FEMALE

PERIOD	DOSE: (mg/kg/day) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY -3	MEAN	18.7	18.8	18.8	18.7
	S.D.	0.91	0.88	0.94	0.83
	N	10	10	10	10
DAY 0	MEAN	20.1	20.1	20.2	19.7
	S.D.	0.81	0.90	0.62	1.14
	N	10	10	10	10
DAY 7	MEAN	21.3	21.4	21.4	21.0
	S.D.	0.76	1.33	0.60	1.05
	N	10	10	10	10
DAY 14	MEAN	22.8	22.6	22.4	21.8
	S.D.	0.90	1.44	0.76	0.83
	N	10	10	10	10
DAY 21	MEAN	23.2	23.3	23.2	22.9
	S.D.	0.60	1.14	0.69	1.04
	N	10	10	10	10
DAY 28	MEAN	23.8	24.1	23.9	23.3
	S.D.	0.57	0.96	0.69	1.06
	N	10	10	10	10
DAY 35	MEAN	24.4	24.6	24.4	23.8
	S.D.	1.07	1.09	0.84	0.93
	N	10	10	10	10
DAY 42	MEAN	24.8	25.2	24.7	24.2
	S.D.	1.01	1.26	1.09	0.97
	N	10	10	10	10
DAY 49	MEAN	24.8	25.4	25.1	24.3
	S.D.	0.86	1.17	0.93	1.25
	N	10	10	10	10
DAY 56	MEAN	25.2	25.7	25.7	24.9
	S.D.	0.97	1.23	0.92	1.28
	N	10	10	10	10

Analysis of Variance using DUNNETT'S Procedure

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 166 SEX: FEMALE

PERIOD	DOSE: (mg/kg/day) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 63	MEAN	26.0	26.8	26.3	25.4
	S.D.	1.23	2.01	0.88	1.47
	N	10	10	10	10
DAY 70	MEAN	26.3	27.1	26.5	25.9
	S.D.	1.38	1.72	1.52	1.69
	N	10	10	10	10
DAY 77	MEAN	26.5	27.3	26.8	26.0
	S.D.	1.16	1.82	1.35	1.33
	N	10	10	10	10
DAY 84	MEAN	26.6	27.6	27.3	26.2
	S.D.	1.46	1.84	1.32	1.10
	N	10	10	10	10
DAY 90	MEAN	27.0	28.2	27.3	26.7
	S.D.	1.69	2.47	1.46	1.21
	N	10	10	10	10

Analysis of Variance using DUNNETT'S Procedure

Table 5.1

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 166 SEX: MALE

PERIOD [a]	DOSE: (mg/kg/day) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 7 [b]	MEAN	1.4	1.2	1.3	0.9
	S.D.	0.55	0.83	0.76	0.74
	N	10	10	10	10
DAY 14	MEAN	0.9	1.4	1.0	1.0
	S.D.	0.74	0.55	0.49	0.26
	N	10	10	10	10
DAY 21	MEAN	0.0	-0.2	-0.1	0.1
	S.D.	0.59	0.56	0.60	0.31
	N	10	10	10	10
DAY 28	MEAN	0.8	0.5	0.5	0.4*
	S.D.	0.30	0.33	0.29	0.21
	N	10	10	10	10
DAY 35	MEAN	0.2	0.5	0.6	0.6
	S.D.	0.40	0.33	0.37	0.34
	N	10	10	10	10
DAY 42	MEAN	0.6	0.6	0.6	0.5
	S.D.	0.37	0.54	0.54	0.14
	N	10	10	10	10
DAY 49	MEAN	0.3	0.2	0.1	0.4
	S.D.	0.69	0.39	0.74	0.34
	N	10	10	10	10
DAY 56	MEAN	0.0	0.4	0.4	0.3
	S.D.	0.40	0.36	0.63	0.46
	N	10	10	10	10
DAY 63	MEAN	0.4	0.2	0.4	0.2
	S.D.	0.73	0.50	0.57	0.62
	N	10	10	10	10
DAY 70	MEAN	0.3	0.6	0.3	0.3
	S.D.	0.43	0.38	0.56	0.32
	N	10	10	10	10

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a] Successive periods

[b] Baseline is day 0

Table 5.1 (contd.)
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 166 SEX: MALE

PERIOD [a]	DOSE: (mg/kg/day) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 77	MEAN	0.2	0.5	0.5	0.2
	S.D.	0.34	0.51	0.75	0.36
	N	10	10	10	10
DAY 84	MEAN	0.2	0.3	0.0	0.3
	S.D.	0.25	0.56	0.48	0.50
	N	10	10	10	10
DAY 90	MEAN	-0.1	0.2	0.3	0.2
	S.D.	0.51	0.34	0.50	0.30
	N	10	10	10	10
TOTAL GAIN	MEAN	5.3	6.1	5.9	5.3
	S.D.	1.33	1.37	1.76	1.25
	N	10	10	10	10

Analysis of Variance using DUNNETT'S Procedure

[a] Successive periods

Table 5.2

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 166 SEX: FEMALE

PERIOD [a]	DOSE: (mg/kg/day) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 7 [b]	MEAN	1.2	1.4	1.2	1.3
	S.D.	0.60	0.64	0.66	0.47
	N	10	10	10	10
DAY 14	MEAN	1.5	1.2	1.0	0.8*
	S.D.	0.57	0.30	0.47	0.45
	N	10	10	10	10
DAY 21	MEAN	0.4	0.6	0.7	1.1*
	S.D.	0.45	0.54	0.50	0.43
	N	10	10	10	10
DAY 28	MEAN	0.5	0.9	0.7	0.5
	S.D.	0.26	0.42	0.65	0.33
	N	10	10	10	10
DAY 35	MEAN	0.6	0.5	0.5	0.5
	S.D.	0.62	0.46	0.87	0.51
	N	10	10	10	10
DAY 42	MEAN	0.4	0.7	0.3	0.3
	S.D.	0.83	0.63	0.75	0.61
	N	10	10	10	10
DAY 49	MEAN	0.0	0.1	0.5	0.1
	S.D.	0.54	0.45	0.70	0.51
	N	10	10	10	10
DAY 56	MEAN	0.4	0.3	0.6	0.6
	S.D.	0.46	0.52	0.51	0.44
	N	10	10	10	10
DAY 63	MEAN	0.8	1.1	0.6	0.5
	S.D.	0.62	1.18	0.62	0.54
	N	10	10	10	10
DAY 70	MEAN	0.4	0.3	0.2	0.5
	S.D.	0.50	0.66	0.89	0.63
	N	10	10	10	10

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a] Successive periods

[b] Baseline is day 0

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 166 SEX: FEMALE

PERIOD [a]	DOSE: (mg/kg/day) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 77	MEAN	0.2	0.3	0.3	0.1
	S.D.	0.64	0.72	0.55	1.06
	N	10	10	10	10
DAY 84	MEAN	0.1	0.3	0.6	0.2
	S.D.	0.68	0.92	0.61	1.20
	N	10	10	10	10
DAY 90	MEAN	0.4	0.6	0.0	0.5
	S.D.	0.69	1.24	0.62	0.82
	N	10	10	10	10
TOTAL GAIN	MEAN	6.9	8.1	7.1	6.9
	S.D.	1.27	1.88	1.12	1.09
	N	10	10	10	10

Analysis of Variance using DUNNETT'S Procedure

[a] Successive periods

Table 6.1

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 166 SEX: MALE

PERIOD[a]	DOSE: (mg/kg/day) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 0[b]	INTAKE (g)	5.3	5.0	5.1	5.0
	S.D.	0.63	0.78	0.94	1.80
	N	10	10	10	10
DAY 7	INTAKE (g)	5.3	5.6	6.2	4.7
	S.D.	0.85	2.30	1.91	1.56
	N	10	10	10	10
DAY 14	INTAKE (g)	5.8	7.7	7.0	7.4
	S.D.	2.18	1.94	1.82	3.36
	N	10	10	10	10
DAY 21	INTAKE (g)	6.9	5.1	4.0*	4.4
	S.D.	4.38	1.59	0.57	0.61
	N	10	10	10	10
DAY 28	INTAKE (g)	4.8	4.6	4.3	4.3
	S.D.	1.08	0.93	0.56	0.47
	N	10	10	10	10
DAY 35	INTAKE (g)	4.5	4.7	4.5	4.5
	S.D.	0.96	0.62	0.86	0.57
	N	10	10	10	10
DAY 42	INTAKE (g)	5.6	6.3	5.4	5.1
	S.D.	1.90	2.04	1.59	1.27
	N	10	10	10	10
DAY 49	INTAKE (g)	4.8	4.9	4.9	4.7
	S.D.	1.22	0.80	1.02	0.55
	N	10	10	10	10

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a] Inclusive intervals

[b] Food in on day -6

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 166 SEX: MALE

PERIOD [a]	DOSE: (mg/kg/day) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 56	INTAKE (g)	4.5	4.4	4.6	4.1
	S.D.	0.77	0.77	0.67	0.34
	N	10	10	10	10
DAY 63	INTAKE (g)	4.1	4.0	3.9	3.6
	S.D.	1.22	0.92	0.57	0.59
	N	10	10	10	10
DAY 70	INTAKE (g)	3.8	3.8	3.7	3.8
	S.D.	0.64	1.04	0.63	0.64
	N	10	10	10	10
DAY 77	INTAKE (g)	4.1	4.5	4.3	4.2
	S.D.	0.81	0.72	0.68	0.69
	N	10	10	10	10
DAY 84	INTAKE (g)	5.0	4.6	4.4	4.4
	S.D.	1.07	1.06	0.98	0.87
	N	10	10	10	10
DAY 90	INTAKE (g)	4.6	4.5	4.4	4.7
	S.D.	1.12	1.21	0.72	0.74
	N	10	10	10	10

Analysis of Variance using DUNNETT'S Procedure

[a] Inclusive intervals

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Table 6.2
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 166 SEX: FEMALE

PERIOD [a]	DOSE: (mg/kg/day) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 0 [b]	INTAKE (g)	5.7	5.1	4.9	5.8
	S.D.	1.89	1.15	1.11	0.53
	N	10	10	10	10
DAY 7	INTAKE (g)	7.9	7.0	9.1	8.4
	S.D.	1.82	2.14	2.86	2.55
	N	10	10	10	10
DAY 14	INTAKE (g)	12.4	8.8	11.5	9.9
	S.D.	3.50	2.83	2.85	2.86
	N	10	10	10	10
DAY 21	INTAKE (g)	11.6	6.3*	5.3*	6.8*
	S.D.	2.70	1.44	1.20	1.14
	N	10	10	10	10
DAY 28	INTAKE (g)	7.2	5.4*	5.2*	5.4*
	S.D.	1.73	0.85	0.74	1.00
	N	10	10	10	10
DAY 35	INTAKE (g)	6.1	5.4	5.3	8.4*
	S.D.	1.10	0.77	0.93	2.52
	N	10	10	10	10
DAY 42	INTAKE (g)	9.1	8.7	8.4	10.6
	S.D.	2.63	1.85	1.47	2.47
	N	10	10	10	10
DAY 49	INTAKE (g)	6.5	6.2	6.3	6.2
	S.D.	0.89	0.85	0.67	1.11
	N	10	10	10	10

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a] Inclusive intervals

[b] Food in on day -6

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SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 166 SEX: FEMALE

PERIOD[a]	DOSE: (mg/kg/day) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 56	INTAKE (g)	5.6	5.9	5.7	6.5
	S.D.	0.72	1.31	1.02	1.82
	N	10	10	10	10
DAY 63	INTAKE (g)	6.4	5.3*	5.2*	4.8*
	S.D.	1.15	0.67	0.50	1.11
	N	10	10	10	10
DAY 70	INTAKE (g)	5.0	4.2	4.2	4.8
	S.D.	0.73	0.69	0.98	0.68
	N	10	10	10	10
DAY 77	INTAKE (g)	5.7	5.9	5.5	5.2
	S.D.	0.94	0.64	0.89	1.30
	N	10	10	10	10
DAY 84	INTAKE (g)	6.8	6.1	5.3*	5.6*
	S.D.	1.15	0.64	1.00	1.40
	N	10	10	10	10
DAY 90	INTAKE (g)	6.1	5.6	5.7	5.9
	S.D.	0.77	0.85	1.02	1.40
	N	10	10	10	10

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

[a] Inclusive intervals

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Table 7.1
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	SDH	TP	ALB	GLOB	A/G	TBA	ALKP	CHOL
UNITS:	IU/L	IU/L	g/dL	g/dL	g/dL	-	umol/L	IU/L	mg/dL
Group: 1-M : 0 mg/kg/day									
MEAN	96	15.2	7.1	3.8	3.3	1.20	33.0	78	91
SD	79.5	5.43	1.61	0.71	0.93	0.133	16.87	15.8	12.4
N	5	5	5	5	5	5	5	5	5
Group: 2-M : 1 mg/kg/day									
MEAN	109	7.7	8.8	5.4**	3.4	2.15	49.0	95	105
SD	12.4	8.71	1.29	0.93	1.42	1.808	13.18	6.3	7.4
N	5	5	5	5	5	5	5	5	5
Group: 3-M : 5 mg/kg/day									
MEAN	120	17.7	6.6	3.5	3.1	1.26	31.3	86	98
SD	138.1	10.58	0.72	0.73	0.87	0.531	15.52	12.3	6.2
N	5	5	5	5	5	5	5	5	5
Group: 4-M : 25 mg/kg/day									
MEAN	172	14.4	5.9	3.1	2.6	1.16	39.6	97	101
SD	120.8	8.11	0.65	0.20	0.15	0.070	14.49	11.1	18.8
N	5	5	5	5	4	4	5	5	5

* Significant Difference from Control P < .05

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	TRIG	BUN	IP	GLU	TSH
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL	ug/ml
Group: 1-M : 0 mg/kg/day					
MEAN	113	22.3	10.5	200	0.09
SD	36.6	2.38	2.99	28.6	0.076
N	5	5	4	5	5
Group: 2-M : 1 mg/kg/day					
MEAN	161	28.0	17.6	170	0.08
SD	32.3	8.04	5.66	21.1	0.050
N	5	5	2	5	5
Group: 3-M : 5 mg/kg/day					
MEAN	130	25.6	14.0	196	0.17
SD	31.8	4.23	3.91	28.3	0.310
N	5	5	4	5	5
Group: 4-M : 25 mg/kg/day					
MEAN	129	26.8	16.2	197	0.16
SD	26.5	1.49	5.18	56.4	0.142
N	5	5	4	5	5

Table 7.2

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	SDH	TP	ALB	GLOB	A/G	TBA	ALKP	CHOL
UNITS:	IU/L	IU/L	g/dL	g/dL	g/dL	-	umol/L	IU/L	mg/dL
Group: 1-F : 0 mg/kg/day									
MEAN	33	23.7	6.6	3.6	2.8	1.30	28.2	118	86
SD	5.9	7.43	0.41	0.36	0.17	0.067	3.08	15.8	7.9
N	5	5	5	5	4	4	5	5	5
Group: 2-F : 1 mg/kg/day									
MEAN	42	22.5	6.5	3.6	3.0	1.22	29.8	119	88
SD	22.7	8.81	0.36	0.28	0.24	0.143	6.31	16.7	7.5
N	5	5	5	5	5	5	5	5	5
Group: 3-F : 5 mg/kg/day									
MEAN	43	26.7	5.9	3.2	2.7	1.17	26.7	126	87
SD	23.5	4.68	0.70	0.38	0.34	0.064	1.37	17.4	8.2
N	5	5	5	5	5	5	5	5	5
Group: 4-F : 25 mg/kg/day									
MEAN	53	25.9	6.1	3.2	2.9	1.12	27.5	126	91
SD	19.0	5.54	0.68	0.37	0.37	0.121	7.87	10.2	10.4
N	5	5	5	5	5	5	5	5	5

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	TRIG	BUN	IP	GLU	TSH
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL	ug/ml
Group: 1-F : 0 mg/kg/day					
MEAN	136	24.9	9.6	178	0.08
SD	44.2	8.10	1.02	20.1	0.049
N	5	5	5	5	5
Group: 2-F : 1 mg/kg/day					
MEAN	128	22.9	10.0	203	0.04
SD	38.2	3.76	1.04	15.7	0.025
N	5	5	5	5	5
Group: 3-F : 5 mg/kg/day					
MEAN	161	25.5	9.3	180	0.03
SD	33.6	2.11	1.51	18.3	0.027
N	5	5	5	5	5
Group: 4-F : 25 mg/kg/day					
MEAN	135	25.7	9.3	211	0.06
SD	23.2	2.48	0.88	42.8	0.037
N	5	5	5	5	5

Table 8.1

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF HEMATOLOGICAL TESTS
PERIOD: WEEK 14

STUDY ID: UIC-11B
STUDY NO: 166
SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC	PLT
UNITS:	10^6/mm^3	g/dL	%	fL	pg	g/dL	% RBCs	COUNT	10^3/mm^3
Group: 1-M : 0 mg/kg/day									
MEAN	10.38	17.6	50.5	48.7	17.0	34.9	0.6	0	962
SD	0.350	0.52	2.00	0.50	0.22	0.43	0.07	0.0	110.2
N	5	5	5	5	5	5	5	5	5
Group: 2-M : 1 mg/kg/day									
MEAN	9.86	16.8	48.0	48.7	17.0	34.9	0.6	0	1049
SD	0.334	0.47	1.60	0.21	0.21	0.48	0.13	0.0	115.3
N	5	5	5	5	5	5	5	5	5
Group: 3-M : 5 mg/kg/day									
MEAN	10.55	17.6	50.4	47.8*	16.7	35.0	0.6	0	1042
SD	0.719	1.07	3.19	0.41	0.26	0.44	0.22	0.0	132.3
N	5	5	5	5	5	5	5	5	5
Group: 4-M : 25 mg/kg/day									
MEAN	10.09	16.3*	45.8*	45.4*	16.1*	35.6	0.4	0	1171
SD	0.371	0.51	1.60	0.62	0.18	0.27	0.17	0.0	80.7
N	5	5	5	5	5	5	5	5	5

*-Significant Difference from Control P < .05

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THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF HEMATOLOGICAL TESTS
PERIOD: WEEK 14

STUDY ID: UIC-11B
STUDY NO: 166

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils
UNITS:	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3
Group: 1-M : 0 mg/kg/day							
MEAN	7.5	1.6	0.0	5.7	0.1	0.1	0.0
SD	2.11	0.79	0.00	1.40	0.14	0.17	0.00
N	5	5	5	5	5	5	5
Group: 2-M : 1 mg/kg/day							
MEAN	6.3	0.9	0.0	5.4	0.D	0.0	D.D
SD	1.52	0.32	0.00	1.39	0.09	0.04	0.00
N	5	5	5	5	5	5	5
Group: 3-M : 5 mg/kg/day							
MEAN	6.8	1.0	0.0	5.7	0.0	0.0	0.0
SO	2.38	0.54	0.00	1.87	0.04	0.04	0.00
N	5	5	5	5	5	5	5
Group: 4-M : 25 mg/kg/day							
MEAN	8.4	1.8	0.0	6.4	0.1	0.1	0.0
SD	2.58	0.94	0.00	2.02	0.08	0.12	0.00
N	5	5	5	5	5	5	5

Table 8.2

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF HEMATOLOGICAL TESTS
PERIOD: WEEK 14

STUDY ID: UIC-11B
STUDY NO: 166

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC	PLT
UNITS:	10^6/mm^3	g/dL	%	fL	pg	g/dL	% RBCs	COUNT	10^3/mm^3
Group: 1-F : 0 mg/kg/day									
MEAN	9.78	17.0	48.2	49.3	17.4	35.4	0.6	0	913
SD	0.238	0.50	1.47	0.38	0.17	0.30	0.11	0.0	181.4
N	5	5	5	5	5	5	5	5	5
Group: 2-F : 1 mg/kg/day									
MEAN	9.77	17.6	48.4	49.5	18.0	36.4	0.5	0	875
SD	0.324	1.24	1.67	0.58	1.26	2.12	0.16	0.0	117.2
N	5	5	5	5	5	5	5	5	5
Group: 3-F : 5 mg/kg/day									
MEAN	9.66	16.8	47.1	48.8	17.4	35.6	0.5	0	958
SD	0.149	0.26	0.70	0.15	0.23	0.34	0.20	0.0	127.8
N	5	5	5	5	5	5	5	5	5
Group: 4-F : 25 mg/kg/day									
MEAN	9.44	16.0	44.3*	47.0*	17.0	36.1	0.4	0	1011
SD	0.179	0.43	1.26	0.49	0.23	0.44	0.19	0.0	68.0
N	5	5	5	5	5	5	5	5	5

*- Significant Difference from Control P < .05

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

SUMMARY OF HEMATOLOGICAL TESTS
PERIOD: WEEK 14

STUDY ID: UIC-118
STUDY NO: 166

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils
UNITS:	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3	10^3/mm^3
Group: 1-F : 0 mg/kg/day							
MEAN	6.7	1.3	0.0	5.2	0.1	0.1	0.0
SD	2.10	0.62	0.04	1.66	0.04	0.05	0.00
N	5	5	5	5	5	5	5
Group: 2-F : 1 mg/kg/day							
MEAN	6.4	0.7	0.0	5.5	0.1	0.1	0.0
SD	0.75	0.33	0.00	0.56	0.04	0.07	0.00
N	5	5	5	5	5	5	5
Group: 3-F : 5 mg/kg/day							
MEAN	5.4	0.8	0.0	4.2	0.1	0.1	0.0
SD	1.13	0.40	0.04	0.84	0.17	0.11	0.00
N	5	5	5	5	5	5	5
Group: 4-F : 25 mg/kg/day							
MEAN	7.7	1.3	0.0	6.3	0.1	0.0	0.0
SD	1.66	0.71	0.00	1.60	0.08	0.04	0.00
N	5	5	5	5	5	5	5

Table 9.1
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 166
SEX: MALE

FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:	(1) 1-M	(2) 2-M	(3) 3-M	(4) 4-M
Heart(% BRAIN WEIGHT)				
MEAN	35.40	38.38	34.61	35.42
SD	3.353	6.196	4.019	3.532
N	10	10	10	10
Kidneys(% BRAIN WEIGHT)				
MEAN	112.84	115.63	112.53	109.89
SD	7.273	10.507	12.483	4.203
N	10	10	10	10
Liver(% BRAIN WEIGHT)				
MEAN	325.77	347.88	329.78	332.39
SD	38.204	32.115	28.663	28.400
N	10	10	10	10
Lungs/Bronchi(% BRAIN WEIGHT)				
MEAN	62.74	61.23	60.95	62.14
SD	10.339	10.384	6.189	8.615
N	10	10	10	10
Spleen(% BRAIN WEIGHT)				
MEAN	14.88	14.67	14.07	14.12
SD	3.024	2.348	2.328	2.057
N	10	10	10	10
Testes(% BRAIN WEIGHT)				
MEAN	51.88	47.84	49.86	51.34
SD	4.073	8.301	5.767	2.392
N	10	10	10	10

(1)-0 mg/kg/day
(2)-1 mg/kg/day
(3)-5 mg/kg/day
(4)-25 mg/kg/day

Table 9.2

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 166
SEX: FEMALE

FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1-F	(6) 2-F	(7) 3-F	(8) 4-F
Heart(% BRAIN WEIGHT)					
	MEAN	29.59	29.68	30.48	30.32
	SD	2.828	3.573	3.399	2.948
	N	10	10	10	10
Kidneys(% BRAIN WEIGHT)					
	MEAN	76.17	76.85	78.21	73.30
	SD	5.218	2.897	4.681	6.352
	N	10	10	10	10
Liver(% BRAIN WEIGHT)					
	MEAN	289.77	299.88	303.67	296.42
	SD	20.201	21.599	14.919	17.957
	N	10	10	10	10
Lungs/Bronchi(% BRAIN WEIGHT)					
	MEAN	56.62	53.17	54.99	50.86
	SD	9.082	9.200	7.935	8.693
	N	10	10	10	10
Spleen(% BRAIN WEIGHT)					
	MEAN	19.16	19.16	19.71	18.45
	SD	2.944	1.874	2.478	3.111
	N	10	10	10	10

(5)-0 mg/kg/day
(6)-1 mg/kg/day
(7)-5 mg/kg/day
(8)-25 mg/kg/day

Table 10

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Summary of Microscopic Lesions

MICROSCOPIC LESIONS[a,b]		Dose (mg/kg/day)			
ORGAN - Lesion	Sex	0	1	5	25
LIVER					
- Glycogen depletion	M	8/10 (1.00)	8/10 (0.90)	10/10 (1.10)	10/10 (1.90)
	F	2/10 (0.20)	2/10 (0.20)	1/10 (0.10)	8/10 (1.30)
- Individual cell necrosis	M	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)
	F	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	2/10 (0.20)

[a]Incidences (mean group severity) - Group mean severity was calculated by dividing the sum of all severity scores for a finding by the number of tissues examined.

[b]Lesion severity was scored as follows:

1 = Minimal 3 = Moderate
2 = Mild 4 = Marked

For additional information see Pathology Report in Appendix 11.

Figure 1

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Summary of Male Body Weights

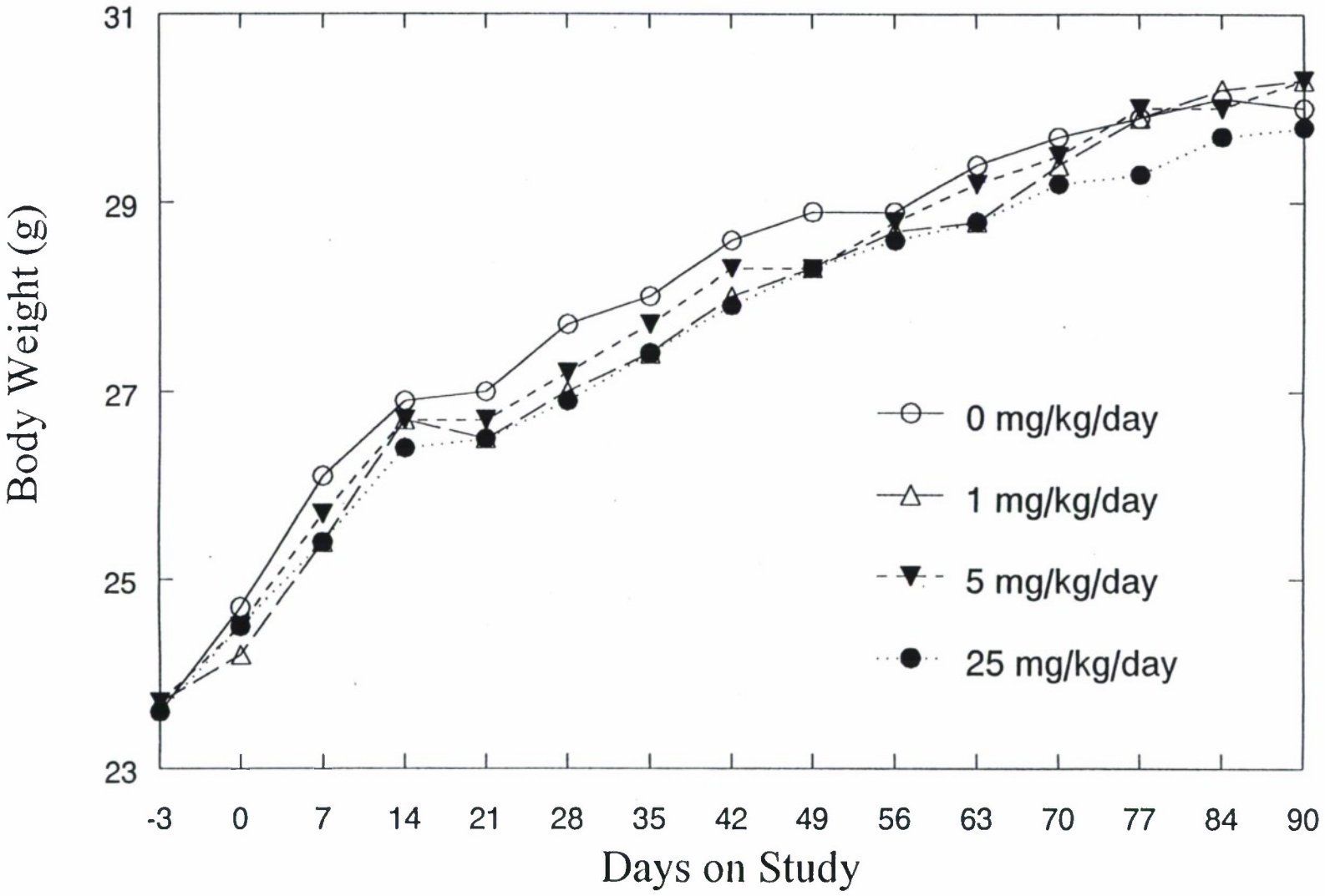


Figure 2

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Summary of Female Body Weights

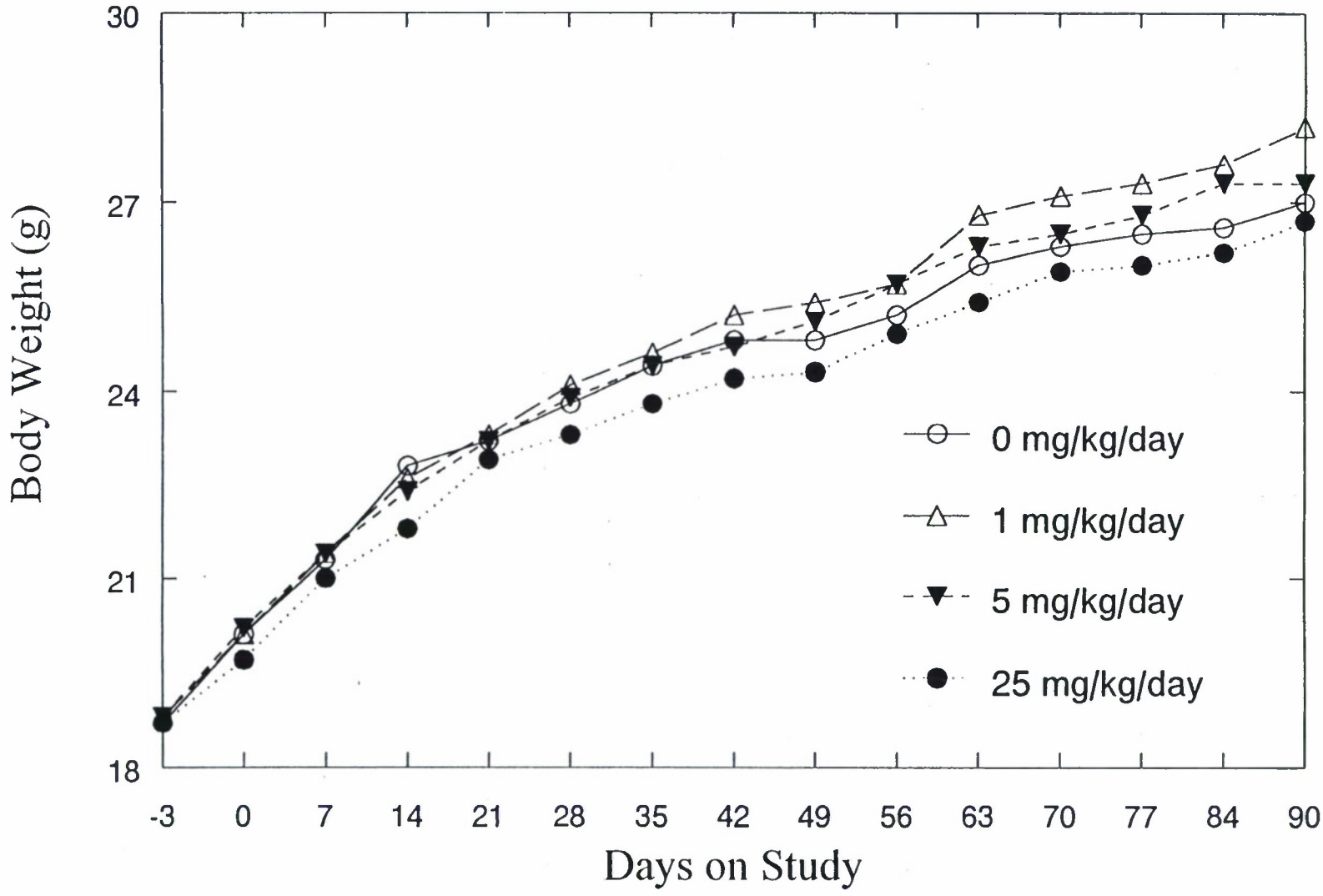
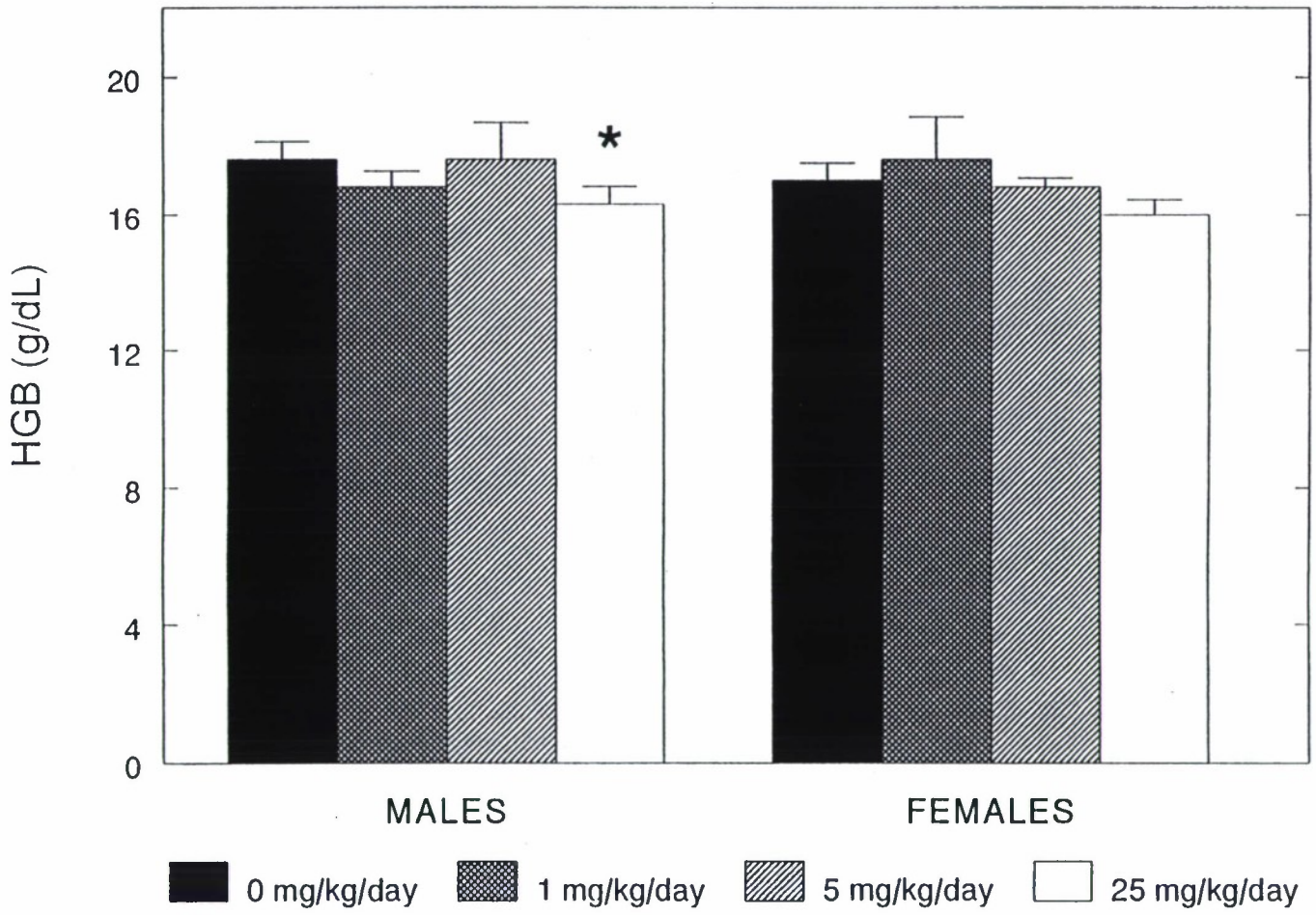


Figure 3

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Summary of Hemoglobin Concentration Data (Days 91/92)

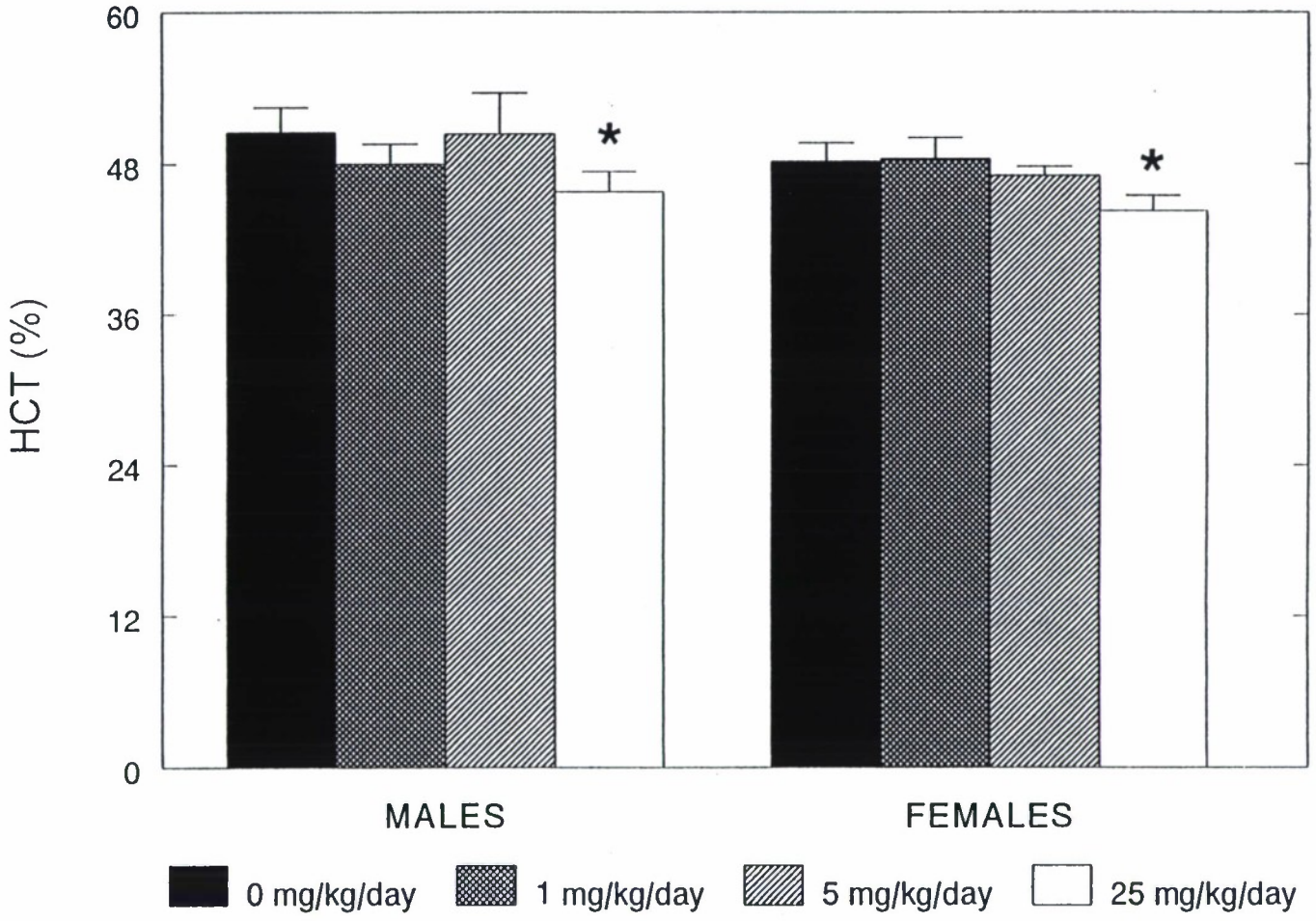


*-Significant Difference from Control p ≤ .05

Figure 4

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Summary of Hematocrit Data (Days 91/92)

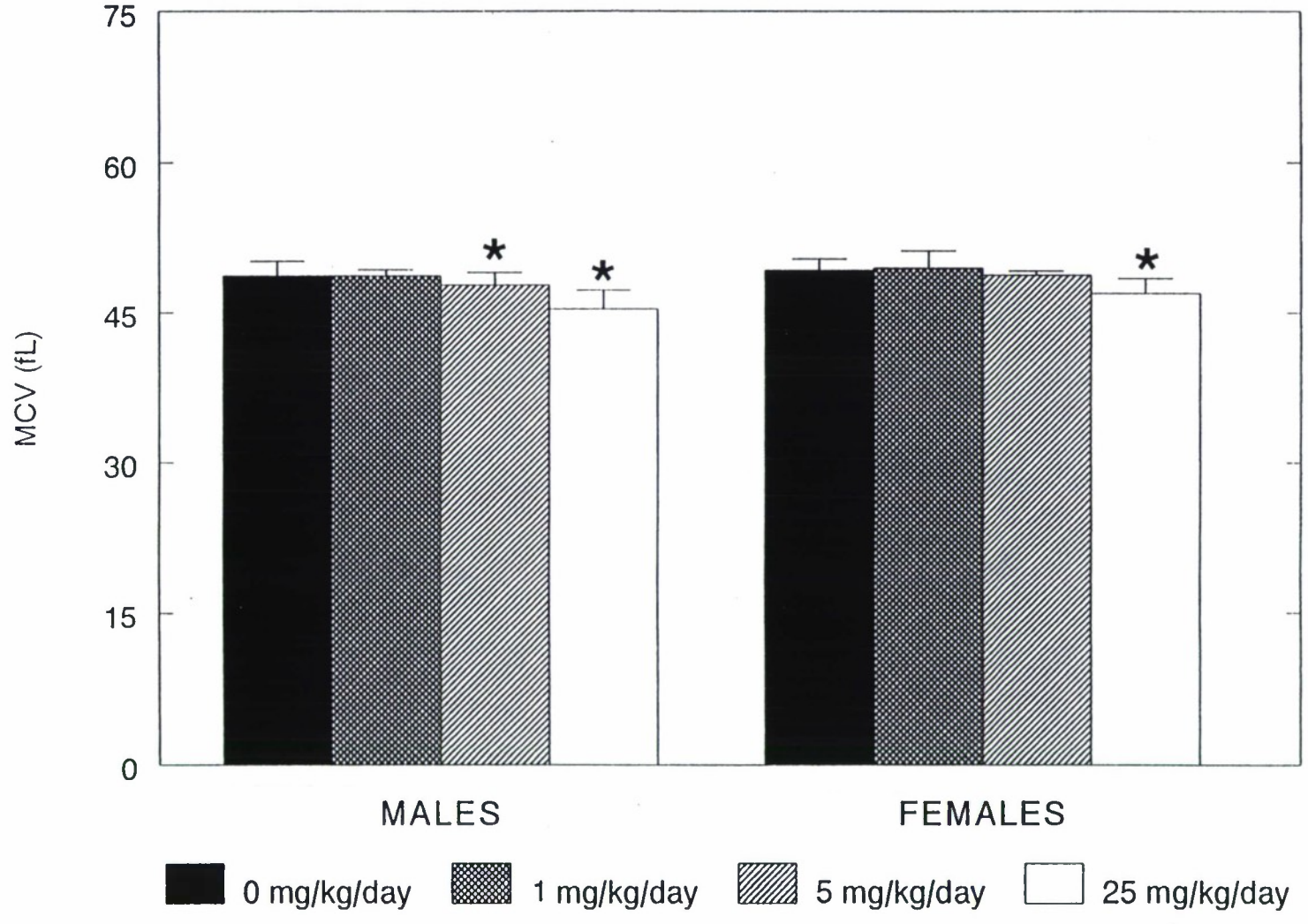


*-Significant Difference from Control p ≤ .05

Figure 5

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Summary of Mean Corpuscular Volume Data (Days 91/92)

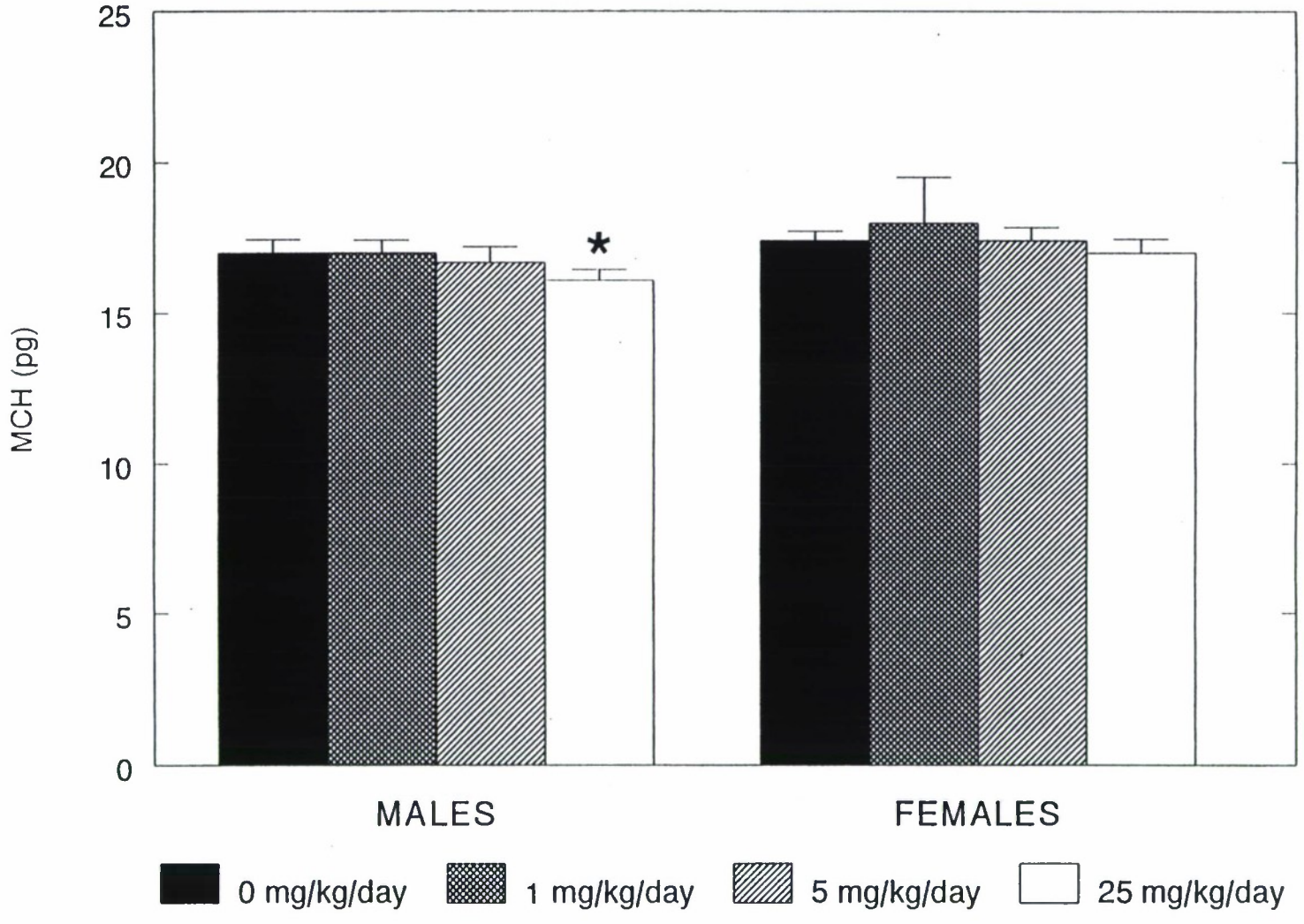


*-Significant Difference from Control $p \leq .05$

Figure 6

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Summary of Mean Corpuscular Hemoglobin Data (Days 91/92)



*-Significant Difference from Control $p \leq .05$

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APPENDIX 1

ANALYTICAL CHEMISTRY REPORT

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THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

UIC/TRL STUDY NUMBER 166

Part I: **Identity and Purity Study of Halofantrine**

Part II: **Assay Precision and Accuracy for the Quantitation of Halofantrine**

Part III: **Dosing Formulations Analysis of Halofantrine in 0.5% Aqueous Methylcellulose**

Analysts: Bozena Libelt
Adam Negrusz
Zaw Kyaw

Study Site: Drug Disposition Research Laboratory
College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois

Sponsor: Toxicology Research Laboratory
University of Illinois at Chicago
Chicago, Illinois

Report Prepared by: Adam Negrusz, Ph.D.
A. Negrusz

Report Prepared: June 12, 1995

Approved: June 12, 1995
Eugene F. Woods, Ph.D.
Laboratory Director
E. Woods 6/12/95

Part I: Identity and Purity Study of Halofantrine

Objective

The objective of this study was to confirm the identity using Nuclear Magnetic Resonance (NMR) spectroscopy and to establish the purity of Halofantrine.

Experimental

The subject sample (Halofantrine) was supplied by the Toxicology Research Laboratory and stored at room temperature until analyzed.

Description

White crystalline powder with no odor.

Identification

Nuclear Magnetic Resonance System

Instrument:	Varian XL-300 FT NMR
Internal Reference:	Tetramethylsilane
Nuclei:	^{1}H, ^{13}C
Acquisition Precision:	Double
Spin Rate (Hz):	20
Temperature:	22°C
Solvent:	Chloroform
Halofantrine Concentration:	400 mg/ml

Pulse Sequence	STD ^{1}H	STD ^{13}C/APT*
Frequency (Mhz)	299.945	75.43
Spectral Width (Hz)	4000	16502
Acquisition Time (s)	3.752	0.909
Relaxation Delay (s)	0.5	1.0
Pulse Width (degrees)	90	90
Decoupling	-	Gated (DM=YYY)
Data Processing:		
FT Size	32K	32K
Line Broadening (Hz)	0.05	0.8
Number of Repetitions	480	1155
Total Time	10 min.	4.5 h

* - Attached Proton Test

Sample Preparation

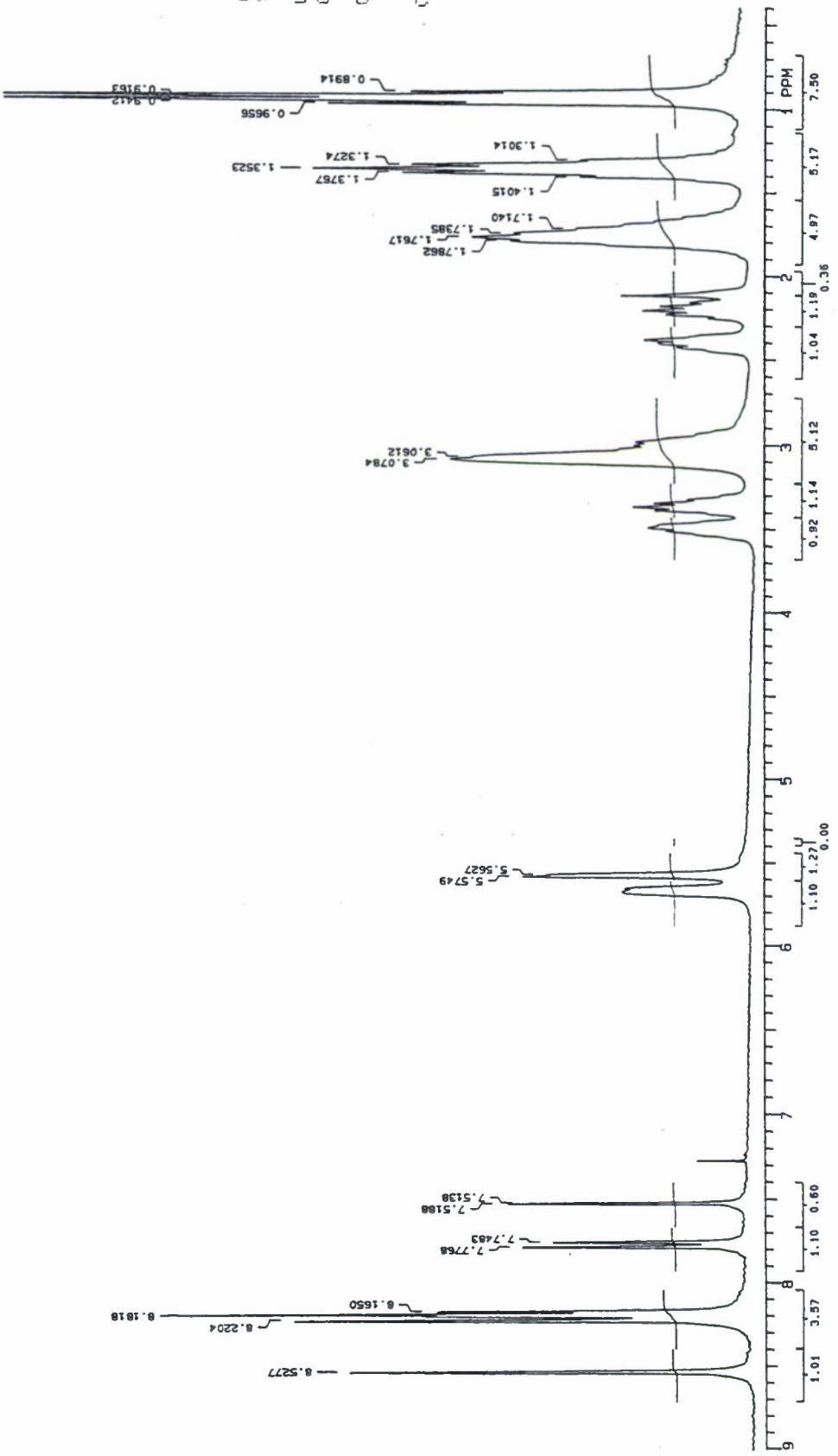
One hundred mg of halofantrine was transferred to a 1.5 ml vial and dissolved in 250 μl of chloroform along with a small drop of tetramethylsilane. The content of the vial was thoroughly mixed and transferred to the instrument for analysis.

Results

The hydrogen spectrum of the test sample is shown in Figure 1. The carbon spectrum for the test sample is shown in Figure 2. The hydrogen and carbon (APT) spectra are consistent with the structure of halofantrine and they are almost identical with those presented in Report No. 676 from January 23, 1990, SRI International Project (Contract No. DAMD17-85-C-5141).

Figure 1

Standard Hydrogen NMR Spectrum for Halofantrine



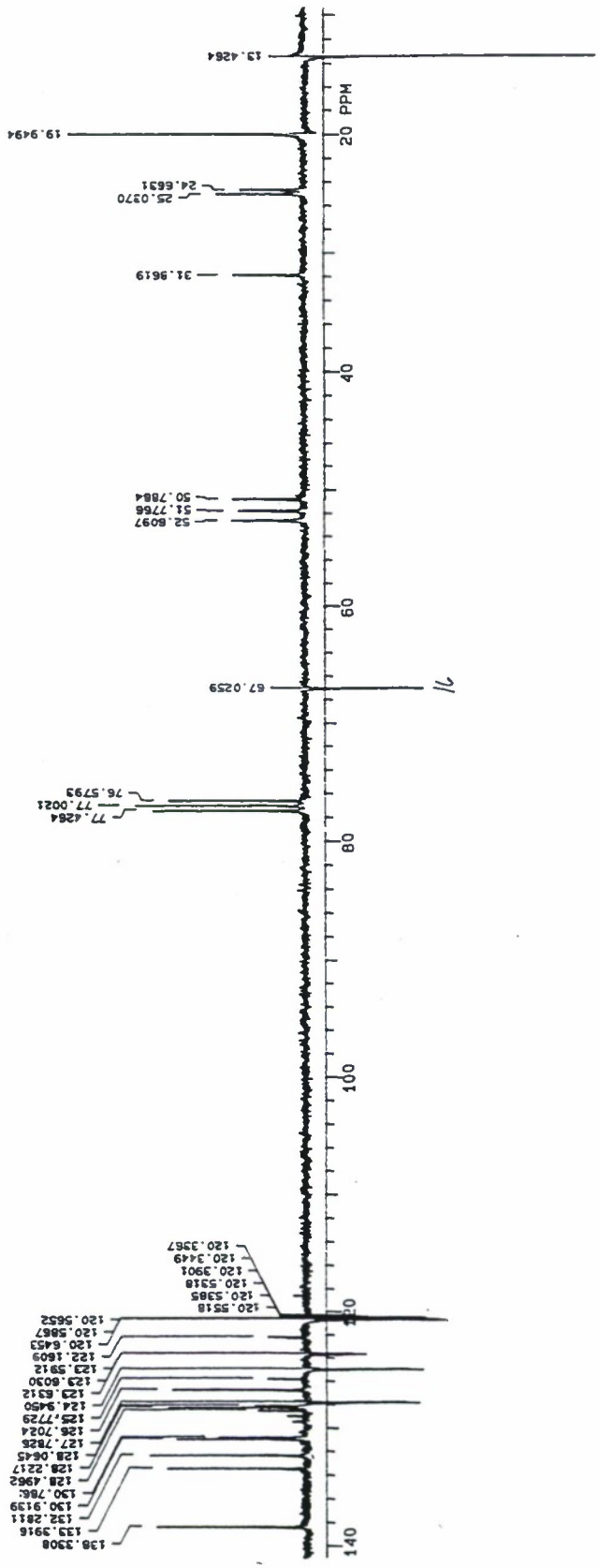


Figure 2

Standard Carbon (APT) NMR Spectrum for Halofantrine

Purity

HPLC System

Solvent Delivery System:	Perkin-Elmer Series 3B Pump
Injector:	Rheodyne 7125 with 50 μl sample loop
Analytical Column:	Hamilton PRP-1, 10 μ, 250 mm x 4.6 mm (Phenomenex)
Detector:	Perkin-Elmer LC-55B UV detector, 258 nm
Integrator:	Spectra-Physics SP4270
Mobile Phase:	30% of deionized water, pH 10 adjusted with 10 % ammonium hydroxide solution in water and 70% of tetrahydrofuran

Procedure

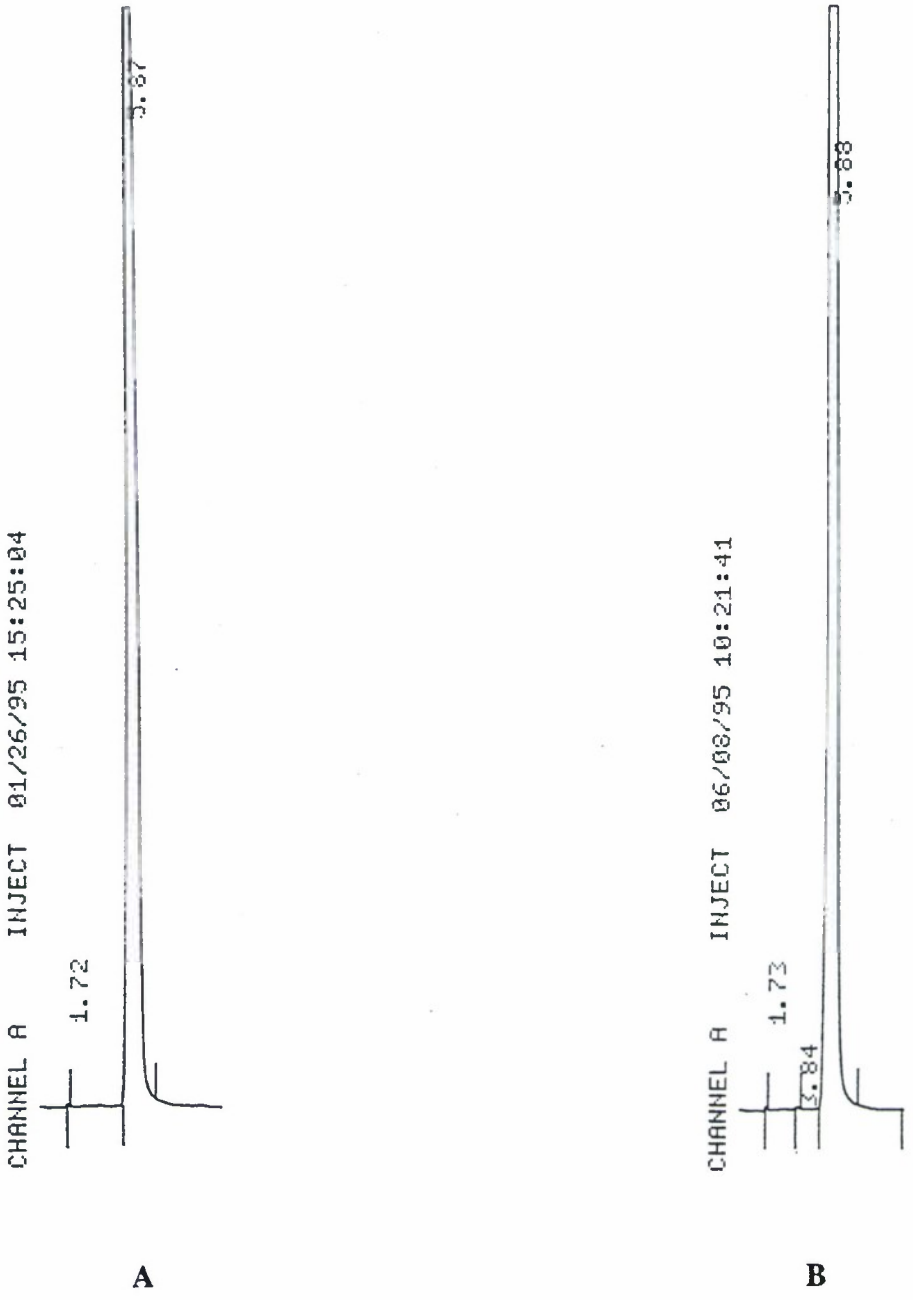
Six solutions of halofantrine were prepared as follows. Twelve and one half mg of halofantrine sample was weighed into a 25 ml volumetric flask. The sample was dissolved in and the volume brought to mark with mobile phase. A 40 μl aliquot of each solution was immediately chromatographed at 258 nm. The same procedure was followed for the initial and terminal samples of halofantrine.

Results

Typical chromatograms are shown in Figure 3. The initial and terminal purity studies of halofantrine show that there are no UV absorbing impurities (258 nm) and from this point of view the substance is 100% pure.

Figure 3

Chromatograms of Halofantrine Sample at 258 nm, Concentration 500 μg/ml
Initial Sample (A) and Terminal Sample (B)



A **B**

Part II: Assay Precision and Accuracy for the Quantitation of Halofantrine

Introduction

The concentrations of halofantrine in mobile phase and in 0.5% aqueous methylcellulose were determined by high performance liquid chromatography (HPLC) using a polymer PRP-1 reverse phase column for separation and UV detection at 258 nm. A standard curve was analyzed twice at the beginning of each assay run and replicate analysis of controls was used to determine intra-day and inter-day variability.

Analytical Method

Reagents

Subject sample (halofantrine hydrochloride) was supplied by the Toxicology Research Laboratory. HPLC grade tetrahydrofuran and ammonium hydroxide (22%) were purchased from Fisher Scientific. HPLC grade water was supplied through a Millipore, Milli-Q^{UF} Plus Water System.

Standards

A 1 mg/ml halofantrine stock solution was prepared by weighing 50 mg of halofantrine hydrochloride into a 50 ml volumetric flask. The content was dissolved in and the volume brought to mark with mobile phase (see Part I). The working halofantrine stock solution (100 μg/ml) was prepared by transferring 5 ml of a 1 mg/ml solution to a 50 ml volumetric flask and diluting to mark with mobile phase. Calibration standard solutions were prepared in mobile phase using a 100 μg/ml working stock solution as follows:

Volume Transferred (ml)	Flask Volume (ml)	Final Concentration (μg/ml)
0.5	10	5
1.0	10	10
2.0	10	20
4.0	10	40
6.0	10	60
8.0	10	80

Controls

Control A (25 μg/ml) was prepared by transferring 25 mg of halofantrine into a 100 ml volumetric flask. The content was dissolved in and diluted to mark with mobile phase. A 1 ml aliquot was next transferred into a 10 ml volumetric flask and diluted to mark with mobile

phase. Control B (50 μg/ml) was prepared by weighing 50 mg of halofantrine into a 100 ml volumetric flask. The content was dissolved in and diluted to mark with mobile phase. A 1 ml aliquot was then transferred into a 10 ml volumetric flask and diluted to mark with mobile phase. Control C (75 μg/ml) was prepared by transferring 75 mg of halofantrine into a 100 ml volumetric flask. The content was dissolved in and diluted to mark with mobile phase. A 1 ml aliquot was then transferred into a 10 ml volumetric flask and diluted to mark with mobile phase. Control solutions were prepared freshly each day just before they were analyzed. Chromatograms of the working solutions are shown in Figure 4.

HPLC System

Solvent Delivery System:	Perkin-Elmer Series 3B Pump
Injector:	Rheodyne 7125 with 50 μl sample loop
Analytical Column:	Hamilton PRP-1, 10 μ, 250 mm x 4.6 mm (Phenomenex)
Detector:	Perkin-Elmer LC-55B UV detector, 258 nm
Integrator:	Spectra-Physics SP4270
Mobile Phase:	30% of deionized water, pH 10 adjusted with 10 % ammonium hydroxide solution in water and 70% of tetrahydofuran

Results

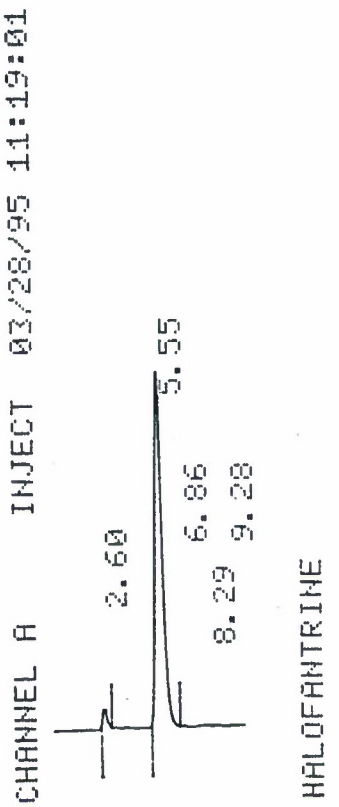
The standard curves were linear over the range of halofantrine assayed (5 μg/ml to 80 μg/ml) and the mean for the regression coefficient was 0.9997 (± 0.0003). A representative standard curve is shown in Figure 5.

Precision and Accuracy

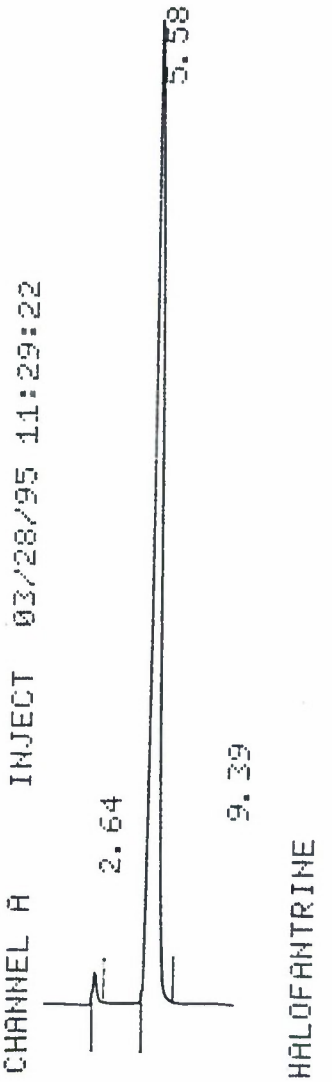
Precision and accuracy were determined using controls at three different concentrations (25 μg/ml, 50 μg/ml and 75 μg/ml). Intra-day variability was determined using six replicates of each control analyzed in a single assay. Inter-day variability was determined over a four day period analyzing replicates of each control solution. The results are summarized in Table 1.

Figure 4

Halofantrine Representative Chromatograms



Control A



Control C

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Figure 5

Standard Curve for Halofantrine

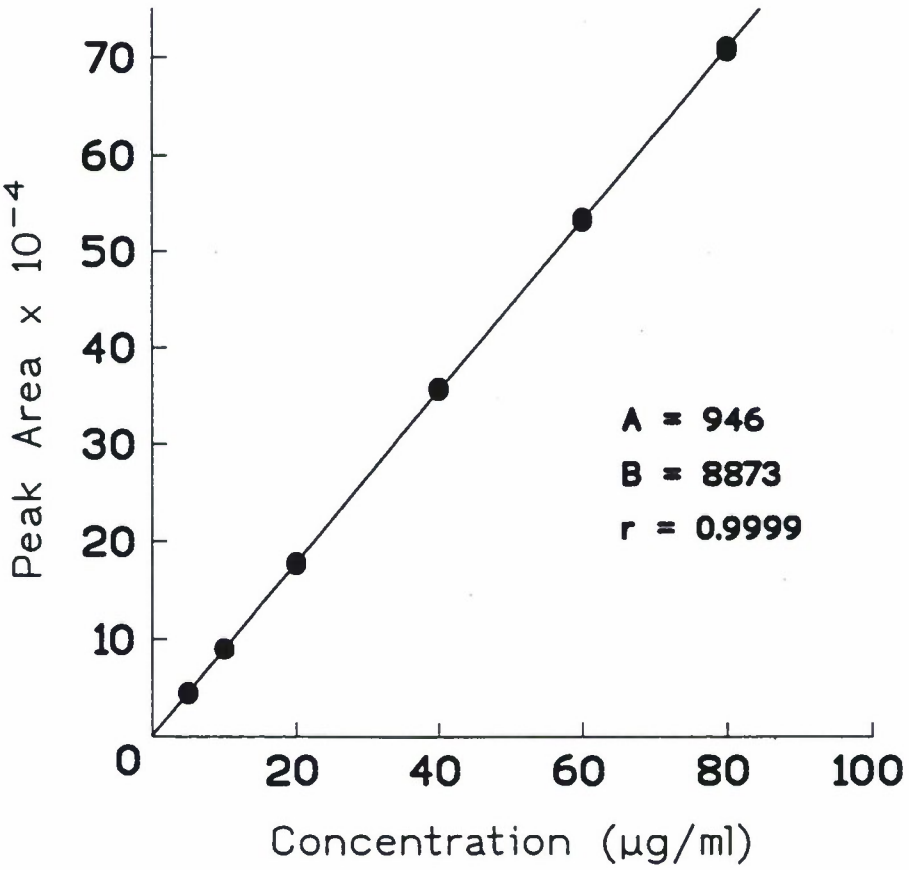

Table 1

Accuracy and Precision of Halofantrine Concentrations (μg/ml)

	Control A	**Control B**	**Control C**
Theoretical concentration	25	50	75
INTRA-DAY (N=6)			
Mean measured conc. (± S.D.)	25.61 (± 0.07)	50.53 (± 0.19)	75.70 (± 0.44)
% coefficient of variation	0.27	0.38	0.58
% relative accuracy	2.44	1.06	0.93
INTER-DAY (N=15)			
Mean measured conc. (± S.D.)	25.58 (± 0.25)	50.24 (± 0.48)	75.82 (± 0.75)
%coefficient of variation	0.98	0.95	0.99
% relative accuracy	2.32	0.48	1.09

Part III: Dosing Formulations Analysis of Halofantrine in 0.5% Aqueous Methylcellulose

Introduction

Samples from Study No. 166 were submitted by the Toxicology Research Laboratory to the Drug Disposition Research Laboratory for the quantitation of halofantrine in dosing formulations. Samples were received on February 14, 1995, February 28, 1995, March 28, 1995, April 18, 1995 and May 9, 1995. All samples submitted were analyzed by high performance liquid chromatography by the previously described analytical method.

Analytical Method

See Part II, Analytical Method.

Results

Results of dosing formulations analysis for Study No. 166 are found in Table 2. All samples used in Study No. 166 were within 10% of their target concentrations.

Table 2

Results of Dosing Solutions Analysis for Study No. 166

Sample Identification	Target Conc. (mg/ml)	2-14-1995 Mean ± S.D.	2-28-1995 Mean ± S.D.	3-28-1995 Mean ± S.D.	4-18-1995 Mean ± S.D.	5-9-1995 Mean ± S.D.
WHITE	0	0	0	0	0	0
YELLOW	0.1	0.1036 ± 0.0008	0.1061 ± 0.0014	0.0997 ± 0.0006	0.1027 ± 0.0012	0.0956 ± 0.0012
BLUE	0.5	0.5430 ± 0.0021	0.4894 ± 0.0029	0.5359 ± 0.0036	0.5199 ± 0.0034	0.4822 ± 0.0048
BLACK	2.5	2.4146 ± 0.0303	2.5414 ± 0.0379	2.5798 ± 0.0166	2.5776 ± 0.0411	2.5136 ± 0.0529

APPENDIX 2

CLINICAL PATHOLOGY METHODOLOGY

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CLINICAL CHEMISTRY

Alanine Aminotransferase (ALT/GPT)

Modified Wroblewski & La Due procedure
Ciba-Corning 550 Express Clinical Chemistry System
Henry, R.J., Chiamori, N., Golub, O.J. and Berkman, S.
Am. J. Clin. Path., 34, 381, 1960.

Sorbitol Dehydrogenase (SDH)

Fructose → Sorbitol oxidase reaction
Ciba-Corning 55 Express Clinical Chemistry System
Asada, M. and Galanbos J.T.
Gastroenterology 44, 578, 1963
Wiesner, I.S. *et al.*
Am. J. dig. Dis. 10, 147, 1965.

Total Protein

Biuret technique
Ciba-Corning 550 Express Clinical Chemistry System
Kingsley, G.R.
J. Biol. Chem. 131, 197, 1939.

Albumin

Bromocresol green method
Ciba-Corning 550 Express Clinical Chemistry System
Doumas, B.T. and Biggs, H.G.
Standard Methods of Clinical Chemistry, 7, 175, 1972.

Total Bile Acids

3α- Hydroxy bile acid oxidation procedure (Sigma Diagnostic kit)
Ciba-Corning 550 Express Clinical Chemistry System
Mashige, F. *et al.*
Clin. Chem. 27, 1352-1356, 1981.

Alkaline Phosphatase

Modified Bessey-Lowry procedure
Ciba-Corning 550 Express Clinical Chemistry System
Neumann, H. and Von Vreedendaal
M. Clin. Chem. Acta., 17, 183, 1967.

Cholesterol

Cholesterol esterase-oxidase method
Ciba-Corning 550 Express Clinical Chemistry System
Rosechlow, P., et. al
Z.F. Klin. Chem. V. Klin. Biochem. 12, 226, 1974.

Triglycerides

Tetrazolium salt reduction method
Ciba-Corning 550 Express Clinical Chemistry System
Klotzsch, S., *et. al.*
Advances Automated Analysis, Vol. 1, Mediad Inc., Tarrytown, N.Y., p. 111, 1973.

Urea Nitrogen (BUN)

Modified urease technique
Ciba-Corning 550 Express Clinical Chemistry System
Talke, H. and Schubert, G.E.
Klin. Wchnschr. 43, 174, 1965.

Phosphorus, Inorganic

Ammonium molybdate method
Ciba-Corning 550 Express Clinical Chemistry System
Fiske, C.H. and Subbarow, Y.
J. Biol. Chem. 66, 325, 1925.

Glucose

Hexokinase method
Ciba-Corning 550 Express Clinical Chemistry System
Bondar, J.L. and Mead, D.C.
Clin. Chem. 20, 586, 1974.

Thyroid Stimulating Hormone

Radioimmunoassay
Polymedco Iso Data Gamma Counter
Ottenweller, J.E. and Hedge, G.A.
Endocrinology 111, 509-514, 1982.

HEMATOLOGY

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Erythrocyte Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Hemoglobin
Cyanomethemoglobin method
Sysmex K1000 Hematology Analyzer

Hematocrit
Indirect method; calculated value based on volume of red cells and volume of blood

Mean Corpuscular Volume (MCV)
Indirect method; calculated value based on hematocrit and red blood cell count

Mean Corpuscular Hemoglobin (MCH)
Indirect method; calculated value based on erythrocyte count and hemoglobin

Mean Corpuscular Hemoglobin Concentration (MCHC)
Indirect method; calculated value based on hematocrit and hemoglobin

Reticulocyte Count
New methylene blue staining procedure
Brecher, G., Am. J. Clin. Path., 19, 895, 1949.

Platelet Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Leukocyte Count
Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Leukocyte Differential Count
Neutrophils - Immature (bands)
Neutrophils - Mature (segs)
Monocytes
Basophils
Lymphocytes
Eosinophils
Wright stain procedure
Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

Nucleated RBCs
Wright stain procedure
Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

RBC Morphology
Wright stain procedure
Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

APPENDIX 3

INDIVIDUAL OBSERVATIONS (CLINICAL SIGNS)

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL CLINICAL SIGNS

STUDY: 166 GROUP: 1-M SEX: MALE
DAY 0-DAY 92 DOSE: 0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
201	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
202	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
203	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
204	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
205	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
206	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
207	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
208	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
209	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
210	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91

INDIVIDUAL CLINICAL SIGNS

STUDY: 166 GROUP: 2-M SEX: MALE
DAY 0-DAY 92 DOSE: 1(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
221	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
222	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
223	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
224	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
225	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
226	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
227	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
228	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
229	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
230	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL CLINICAL SIGNS

STUDY: 166 GROUP: 3-M SEX: MALE
DAY 0-DAY 92 DOSE: 5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
241	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
242	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
243	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
244	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
245	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
246	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
247	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
248	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
249	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
250	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL CLINICAL SIGNS

STUDY: 166 GROUP: 4-M SEX: MALE
DAY 0-DAY 92 DOSE: 25(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
261	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
262	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
263	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
264	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
265	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
266	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
267	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
268	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
269	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
270	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL CLINICAL SIGNS

STUDY: 166 GROUP: 1-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
211	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
212	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
213	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
214	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
215	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
216	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
217	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
218	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
219	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
220	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL CLINICAL SIGNS

STUDY: 166 GROUP: 2-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 1(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
231	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
232	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
233	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
234	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
235	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
236	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
237	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
238	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
239	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
240	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92

INDIVIDUAL CLINICAL SIGNS

STUDY: 166 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
251	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
252	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
253	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
254	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
255	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
256	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
257	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
258	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
259	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
260	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92

INDIVIDUAL CLINICAL SIGNS

STUDY: 166 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 25(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
271	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
272	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
273	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
274	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
275	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
276	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
277	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
278	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
279	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
280	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 0					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 1					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 2					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 3					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 4					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 5					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
OAY 6					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
OAY 7					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 8					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 9					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 10					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 11					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 12					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 13					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 14					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 15					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 16					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 17					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 18					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 19					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: MALE

PERIOD		DOSE:(mg/kg) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 20	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 21					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 22					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 23					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 24					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 25					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 26					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 27					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 28					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 29					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 30					
	No. Observed		10	10	10	10

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: MALE

	PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 30 (contd.)	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 31					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 32					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 33					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 34					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 35					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 36					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 37					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 38					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 39					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
	DAY 40					
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 41					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 42					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 43					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 44					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 45					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 46					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 47					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 48					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 49					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 50					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 51					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 52					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 53					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 54					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 55					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 56					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 57					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 58					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 59					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 60					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: MALE

PERIOD		DOSE:(mg/kg) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 61	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
DAY 62						
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
DAY 63						
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
DAY 64						
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
DAY 65						
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
DAY 66						
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
DAY 67						
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
DAY 68						
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
DAY 69						
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
DAY 70						
	No. Observed		10	10	10	10
	Normal		10 100%	10 100%	10 100%	10 100%
DAY 71						
	No. Observed		10	10	10	10

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 71 (contd.)	Normal	10 100%	10 100%	10 100%	10 100%
DAY 72					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 73					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 74					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 75					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 76					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 77					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 78					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 79					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 80					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 81					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	1 2-M	5 3-M	25 4-M
DAY 82					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 83					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 84					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 85					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 86					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 87					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 88					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 89					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 90					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 91					
	No. Observed	10	10	10	10
	Scheduled Sacrifice	10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 0					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 1					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 2					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 3					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 4					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 5					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 6					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 7					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 8					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 9					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 10					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 11					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 12					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 13					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 14					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 15					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 16					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 17					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 18					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 19					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 20	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 21					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 22					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 23					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 24					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 25					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 26					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 27					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 28					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 29					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 30					
	No. Observed	10	10	10	10

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 30 (contd.)	Normal	10 100%	10 100%	10 100%	10 100%
DAY 31					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 32					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 33					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 34					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 35					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 36					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 37					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 38					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 39					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 40					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: FEMALE

PERIOD	OOSE:(mg/kg) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 41					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 42					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 43					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 44					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 45					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 46					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
OAY 47					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
OAY 48					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 49					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
OAY 50					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 51					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 52					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 53					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 54					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 55					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 56					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 57					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 58					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 59					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 60					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 61	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 62					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 63					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 64					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 65					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 66					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 67					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 68					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 69					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 70					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 71					
	No. Observed	10	10	10	10

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 71 (contd.)	Normal	10 100%	10 100%	10 100%	10 100%
	DAY 72				
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
	DAY 73				
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
	DAY 74				
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
	DAY 75				
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
	DAY 76				
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
	DAY 77				
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
	DAY 78				
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
	DAY 79				
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
	DAY 80				
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
	DAY 81				
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%

INCIDENCE OF OBSERVATIONS

STUDY: 166 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	1 2-F	5 3-F	25 4-F
DAY 82					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 83					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 84					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 85					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 86					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 87					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 88					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 89					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 90					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 91					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	10 100%
DAY 92					
	No. Observed	10	10	10	10
	Scheduled Sacrifice	10 100%	10 100%	10 100%	10 100%

DRAFT

APPENDIX 4

INDIVIDUAL BODY WEIGHT AND BODY WEIGHT GAIN DATA

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 1-M SEX: MALE
DOSE: 0(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
201	23.0	23.9	25.3	26.5	26.2	26.5	26.2	27.3	26.8	26.9	27.1	27.2
202	23.8	24.7	25.9	26.2	26.8	27.2	27.4	28.1	28.6	28.5	28.9	29.3
203	22.9	24.9	26.6	27.9	28.2	29.5	29.0	29.0	29.1	29.8	30.8	30.3
204	24.3	25.8	26.1	27.3	27.9	28.9	28.9	29.4	30.3	29.7	29.7	30.1
205	24.1	24.7	26.6	26.9	27.6	28.4	28.9	29.7	29.1	29.4	30.7	31.3
206	23.0	24.3	25.0	26.4	25.9	26.5	26.8	27.3	28.2	28.5	27.9	28.4
207	23.5	24.7	26.0	25.3	25.9	26.9	27.7	28.5	28.9	28.9	29.4	29.9
208	24.7	25.1	26.7	27.6	26.7	27.7	28.1	28.3	29.7	29.7	30.7	31.7
209	23.5	24.4	26.1	26.9	26.4	27.1	27.7	28.0	28.7	28.1	27.4	28.0
210	23.6	24.3	26.4	28.3	28.0	28.7	29.1	30.2	29.7	29.9	31.2	31.0
MEAN	23.6	24.7	26.1	26.9	27.0	27.7	28.0	28.6	28.9	28.9	29.4	29.7
S.D.	0.60	0.52	0.56	0.89	0.89	1.07	1.00	0.98	0.96	0.96	1.51	1.48
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 1-M SEX: MALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 77	DAY 84	DAY 90
201	27.5	27.4	27.3
202	29.2	29.5	28.9
203	30.7	30.9	31.0
204	29.8	30.1	30.0
205	31.6	32.2	31.6
206	28.7	28.5	29.6
207	29.6	29.8	29.6
208	32.1	32.5	31.8
209	28.7	28.8	28.5
210	30.9	31.4	31.4
MEAN	29.9	30.1	30.0
S.D.	1.44	1.65	1.48
N	10	10	10

--: Data Unavailable

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 2-M SEX: MALE
DOSE: 1(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
221	25.0	25.3	26.3	27.7	26.9	27.5	27.7	28.5	29.0	29.2	28.5	29.1
222	23.1	24.5	24.4	26.2	25.2	25.3	25.3	26.8	26.9	26.9	27.3	27.6
223	23.5	24.1	25.1	26.5	26.7	27.3	27.9	28.7	28.5	29.4	30.3	31.3
224	23.0	23.6	25.4	26.6	25.9	26.6	26.5	27.0	27.9	28.1	28.1	28.9
225	22.5	23.2	24.4	24.6	25.4	26.5	27.3	27.8	27.8	28.1	28.2	28.7
226	23.8	24.1	24.9	26.9	26.3	27.0	27.8	28.8	29.3	29.4	30.0	31.2
227	24.1	23.4	26.3	27.5	27.7	27.8	28.2	28.0	28.3	29.0	28.7	28.9
228	24.5	25.5	25.7	27.8	27.5	27.6	28.4	28.2	28.1	29.1	28.8	29.2
229	23.3	23.7	25.2	26.5	26.6	26.9	27.5	27.9	28.5	28.8	29.2	29.3
230	24.1	24.6	25.8	26.8	26.7	27.2	27.6	28.7	28.4	28.5	29.1	30.1
MEAN	23.7	24.2	25.4	26.7	26.5	27.0	27.4	28.0	28.3	28.7	28.8	29.4
S.D.	0.76	0.78	0.69	0.92	0.82	0.72	0.91	0.70	0.67	0.78	0.89	1.14
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 2-M SEX: MALE
DOSE: 1(mg/kg)

ANIMAL #	DAY 77	DAY 84	DAY 90
221	29.4	29.7	29.9
222	28.7	29.8	29.4
223	32.2	32.0	32.5
224	30.0	30.6	30.4
225	29.4	29.0	29.7
226	31.0	31.4	31.7
227	29.5	30.1	30.3
228	29.0	29.9	29.7
229	29.9	29.4	29.7
230	30.0	29.8	29.9
MEAN	29.9	30.2	30.3
S.D.	1.02	0.92	1.00
N	10	10	10

--: Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 3-M SEX: MALE
DOSE: 5(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
241	23.2	24.0	23.4	25.0	24.0	25.0	25.4	25.9	25.9	26.3	26.5	26.8
242	24.2	25.0	26.3	27.8	27.4	27.5	27.9	27.5	28.3	28.2	29.0	28.6
243	24.6	24.9	26.4	27.6	27.1	27.7	28.1	28.4	29.2	29.3	30.2	30.7
244	24.3	25.4	26.5	26.7	27.3	27.8	27.9	29.0	29.0	29.0	29.2	29.0
245	23.0	24.7	26.5	26.8	26.8	27.2	27.7	28.6	28.6	28.9	28.7	30.2
246	23.0	23.8	25.7	26.7	27.7	28.3	28.9	28.7	28.5	29.9	29.7	30.5
247	23.7	23.8	24.7	26.1	26.5	26.6	27.3	27.9	28.9	28.5	28.5	28.9
248	22.9	24.3	25.3	25.9	26.0	26.2	26.7	27.7	27.5	27.8	28.5	28.5
249	23.7	24.2	25.7	26.7	26.1	26.5	27.0	27.5	27.6	28.4	28.6	29.0
250	23.9	24.7	26.8	28.0	27.9	28.7	30.2	31.4	29.8	31.3	32.9	32.7
MEAN	23.7	24.5	25.7	26.7	26.7	27.2	27.7	28.3	28.3	28.8	29.2	29.5
S.D.	0.61	0.54	1.04	0.92	1.14	1.10	1.29	1.41	1.10	1.32	1.63	1.60
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 3-M SEX: MALE
DOSE: 5(mg/kg)

ANIMAL #	DAY 77	DAY 84	DAY 90
241	27.0	27.2	27.8
242	28.5	29.0	29.2
243	31.7	30.8	31.0
244	30.0	30.5	30.5
245	30.1	30.1	29.6
246	30.4	30.7	30.8
247	29.1	29.3	30.6
248	28.7	28.4	29.3
249	29.5	29.7	29.9
250	35.0	34.3	34.6
MEAN	30.0	30.0	30.3
S.D.	2.16	1.88	1.78
N	10	10	10

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 4-M SEX: MALE
DOSE: 25(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
261	23.8	23.7	25.6	26.4	27.0	27.4	27.8	28.4	29.3	29.6	28.7	29.4
262	22.3	23.4	24.2	25.2	25.1	25.3	25.9	26.1	26.7	26.4	27.1	27.1
263	24.9	25.5	26.1	27.4	27.6	27.9	28.3	28.9	29.3	29.4	29.9	30.7
264	24.6	25.8	25.8	27.2	27.4	27.9	28.9	29.5	29.6	30.4	30.6	31.0
265	23.1	24.0	25.0	25.8	25.9	26.1	26.4	26.9	27.8	28.3	27.5	28.2
266	23.0	23.0	23.7	24.2	24.6	25.5	25.4	25.7	26.0	27.1	27.2	27.3
267	23.6	25.7	25.4	26.4	26.7	26.9	27.7	28.2	28.1	28.3	29.0	29.0
268	23.3	24.4	25.4	26.4	26.0	26.3	27.0	27.5	27.8	28.3	28.6	28.6
269	23.7	25.0	26.6	27.4	27.3	27.7	28.3	28.6	28.7	28.3	29.3	29.4
270	24.1	24.6	26.5	27.6	27.3	27.7	28.7	29.2	29.8	30.3	30.5	30.8
MEAN	23.6	24.5	25.4	26.4	26.5	26.9	27.4	27.9	28.3	28.6	28.8	29.2
S.D.	0.77	0.99	0.93	1.09	1.04	1.00	1.21	1.30	1.27	1.30	1.28	1.40
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 4-M SEX: MALE
DOSE: 25(mg/kg)

ANIMAL #	DAY 77	DAY 84	DAY 90
261	29.3	30.2	30.9
262	27.7	27.6	27.9
263	30.8	30.4	30.3
264	31.0	31.8	32.0
265	28.5	29.0	28.9
266	26.7	27.7	27.4
267	29.3	29.7	29.7
268	29.1	28.9	29.2
269	29.6	29.5	29.6
270	31.3	31.7	32.2
MEAN	29.3	29.7	29.8
S.D.	1.46	1.44	1.59
N	10	10	10

--: Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
211	19.1	20.9	21.7	22.5	23.4	24.0	24.4	23.9	24.5	25.3	25.3	26.2
212	19.3	20.7	21.1	23.8	24.0	23.9	24.3	26.2	25.9	25.8	26.3	27.5
213	20.3	21.2	22.4	23.7	23.9	24.6	26.7	25.5	25.6	27.0	28.2	28.5
214	18.5	19.5	21.1	22.5	22.7	23.4	23.7	23.7	23.4	23.7	24.6	24.8
215	18.2	19.7	21.4	22.6	22.8	23.5	24.6	25.4	24.3	25.1	26.3	27.1
216	18.7	19.7	21.2	22.1	22.5	23.3	23.9	24.6	24.5	24.5	25.9	25.4
217	18.0	19.7	20.2	22.1	22.8	23.2	23.0	23.2	24.0	24.5	24.6	25.0
218	19.8	21.2	22.6	24.6	24.2	24.9	25.6	26.0	25.9	26.3	27.8	28.2
219	17.7	18.9	21.2	22.4	23.0	23.4	23.6	24.3	24.3	24.6	25.6	25.6
220	17.5	19.7	20.4	21.9	23.1	23.6	24.1	24.8	25.3	25.3	25.1	25.1
MEAN	18.7	20.1	21.3	22.8	23.2	23.8	24.4	24.8	24.8	25.2	26.0	26.3
S.D.	0.91	0.81	0.76	0.90	0.60	0.57	1.07	1.01	0.86	0.97	1.23	1.38
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 77	DAY 84	DAY 90
211	27.0	26.8	26.4
212	27.9	28.7	30.0
213	28.0	29.4	29.2
214	24.5	24.8	24.9
215	26.3	25.8	26.2
216	25.7	25.6	26.0
217	25.6	25.4	25.4
218	27.9	26.9	28.5
219	26.2	26.0	26.9
220	26.3	26.6	26.3
MEAN	26.5	26.6	27.0
S.D.	1.16	1.46	1.69
N	10	10	10

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 2-F SEX: FEMALE
DOSE: 1(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
231	20.4	21.1	23.1	24.9	24.4	24.8	25.9	26.6	26.0	25.6	28.8	29.1
232	17.5	18.7	19.4	20.6	21.3	22.8	23.9	23.5	23.3	23.5	24.4	24.8
233	19.0	20.1	21.4	22.6	23.3	24.2	24.3	25.3	25.3	25.9	26.0	26.6
234	18.6	20.3	20.6	22.2	23.4	24.3	24.3	24.8	25.6	25.2	25.7	26.1
235	19.3	20.7	22.5	23.6	23.6	24.3	25.2	27.0	26.5	26.8	28.4	28.7
236	17.9	19.2	20.3	21.1	21.7	23.0	23.1	23.7	24.0	24.7	24.6	26.3
237	18.2	19.5	20.2	21.2	22.6	23.2	23.1	23.9	24.3	24.4	24.4	25.0
238	19.0	20.1	22.3	23.6	24.2	24.3	25.0	26.2	26.6	26.7	29.6	29.5
239	19.8	21.6	23.3	24.3	24.9	26.1	26.4	26.2	26.7	27.4	28.7	28.4
240	18.3	19.4	21.2	22.3	23.1	24.0	24.5	25.2	25.2	26.5	26.9	26.1
MEAN	18.8	20.1	21.4	22.6	23.3	24.1	24.6	25.2	25.4	25.7	26.8	27.1
S.D.	0.88	0.90	1.33	1.44	1.14	0.96	1.09	1.26	1.17	1.23	2.01	1.72
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 2-F SEX: FEMALE
DOSE: 1(mg/kg)

ANIMAL #	DAY 77	DAY 84	DAY 90
231	28.8	27.7	29.9
232	24.8	24.9	25.7
233	26.3	26.7	26.7
234	27.7	28.3	27.3
235	29.2	29.7	32.5
236	25.7	25.8	25.5
237	26.0	25.7	25.5
238	29.7	28.8	30.4
239	29.4	30.6	30.4
240	25.8	27.8	27.8
MEAN	27.3	27.6	28.2
S.D.	1.82	1.84	2.47
N	10	10	10

--: Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 3-F SEX: FEMALE
DOSE: 5(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
251	17.8	19.9	20.8	22.4	23.2	23.4	23.9	24.4	24.8	24.9	25.1	25.4
252	18.1	19.4	21.3	21.5	22.6	23.1	23.3	23.5	23.6	24.8	24.9	24.9
253	18.3	19.2	20.6	21.6	22.2	22.9	23.6	24.1	24.2	25.2	25.4	24.2
254	19.0	20.1	22.2	22.8	23.1	23.3	26.0	24.9	25.2	24.9	26.8	27.1
255	18.7	19.9	21.7	22.8	23.2	23.6	24.6	25.1	24.8	25.1	26.3	26.4
256	19.4	20.1	21.3	22.1	23.0	24.4	24.4	25.4	25.7	26.4	26.7	27.1
257	17.2	20.9	20.9	22.3	24.2	24.1	24.5	24.8	25.9	26.5	27.2	26.6
258	20.0	20.8	21.9	22.9	23.1	24.1	23.5	22.8	25.0	25.5	26.4	26.6
259	20.1	21.0	22.3	24.0	24.4	25.0	25.3	26.8	27.0	27.4	27.5	29.8
260	19.1	20.6	21.0	21.7	22.5	24.6	24.7	24.8	25.2	26.6	26.6	26.6
MEAN	18.8	20.2	21.4	22.4	23.2	23.9	24.4	24.7	25.1	25.7	26.3	26.5
S.D.	0.94	0.62	0.60	0.76	0.69	0.69	0.84	1.09	0.93	0.92	0.88	1.52
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 3-F SEX: FEMALE
DOSE: 5(mg/kg)

ANIMAL #	DAY 77	DAY 84	DAY 90
251	26.0	25.7	25.9
252	25.0	25.6	25.8
253	25.3	26.8	25.8
254	26.9	28.0	28.2
255	26.3	26.1	26.6
256	27.1	28.3	28.3
257	28.0	28.6	27.5
258	26.6	27.3	27.2
259	29.7	29.6	30.5
260	26.8	27.2	27.0
MEAN	26.8	27.3	27.3
S.D.	1.35	1.32	1.46
N	10	10	10

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 4-F SEX: FEMALE
DOSE: 25(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
271	18.6	20.4	22.3	22.5	23.7	24.6	24.5	24.3	24.3	25.1	24.9	25.7
272	19.6	20.6	21.4	21.8	22.2	23.0	24.0	24.1	24.2	24.7	25.6	26.1
273	18.9	19.2	21.2	22.0	22.8	23.1	23.6	25.2	25.1	25.6	25.6	26.7
274	19.2	20.0	21.0	21.7	23.1	23.2	23.2	23.6	24.6	24.7	25.2	25.7
275	17.9	17.7	19.6	21.3	21.8	21.7	22.6	22.6	22.5	23.2	23.5	24.2
276	18.2	19.5	20.6	21.7	22.7	23.4	24.0	23.9	24.1	25.3	26.3	25.8
277	18.3	18.9	19.9	20.8	22.2	22.9	24.4	24.4	23.9	24.5	25.9	26.4
278	20.2	21.7	22.6	23.5	25.0	25.3	25.4	26.1	27.1	27.5	28.4	29.9
279	19.1	20.4	21.7	21.9	23.6	23.9	24.3	24.0	23.9	25.3	25.2	24.7
280	17.4	18.8	19.7	20.6	21.5	22.2	22.3	23.3	22.9	22.9	23.1	23.8
MEAN	18.7	19.7	21.0	21.8	22.9	23.3	23.8	24.2	24.3	24.9	25.4	25.9
S.D.	0.83	1.14	1.05	0.83	1.04	1.06	0.93	0.97	1.25	1.28	1.47	1.69
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 166 GROUP: 4-F SEX: FEMALE
DOSE: 25(mg/kg)

ANIMAL #	DAY 77	DAY 84	DAY 90
271	25.6	26.8	25.8
272	25.8	25.9	26.4
273	27.4	26.5	27.5
274	27.8	25.6	27.2
275	24.4	24.9	25.2
276	25.6	27.3	27.5
277	26.6	26.3	27.0
278	27.7	27.7	28.9
279	25.2	26.9	26.1
280	24.0	24.1	24.9
MEAN	26.0	26.2	26.7
S.D.	1.33	1.10	1.21
N	10	10	10

--: Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 1-M SEX: MALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 7 [b]	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
201	1.4	1.2	-0.3	0.3	-0.3	1.1	-0.5	0.1	0.2	0.1	0.3
202	1.2	0.3	0.6	0.4	0.2	0.7	0.5	-0.1	0.4	0.4	-0.1
203	1.7	1.3	0.3	1.3	-0.5	0.0	0.1	0.7	1.0	-0.5	0.4
204	0.3	1.2	0.6	1.0	0.0	0.5	0.9	-0.6	0.0	0.4	-0.3
205	1.9	0.3	0.7	0.8	0.5	0.8	-0.6	0.3	1.3	0.6	0.3
206	0.7	1.4	-0.5	0.6	0.3	0.5	0.9	0.3	-0.6	0.5	0.3
207	1.3	-0.7	0.6	1.0	0.8	0.8	0.4	0.0	0.5	0.5	-0.3
208	1.6	0.9	-0.9	1.0	0.4	0.2	1.4	0.0	1.0	1.0	0.4
209	1.7	0.8	-0.5	0.7	0.6	0.3	0.7	-0.6	-0.7	0.6	0.7
210	2.1	1.9	-0.3	0.7	0.4	1.1	-0.5	0.2	1.3	-0.2	-0.1
MEAN	1.4	0.9	0.0	0.8	0.2	0.6	0.3	0.0	0.4	0.3	0.2
S.D.	0.55	0.74	0.59	0.30	0.40	0.37	0.69	0.40	0.73	0.43	0.34
N	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 84	DAY 90	TOTAL GAIN
201	-0.1	-0.1	3.4
202	0.3	-0.6	4.2
203	0.2	0.1	6.1
204	0.3	-0.1	4.2
205	0.6	-0.6	6.9
206	-0.2	1.1	5.3
207	0.2	-0.2	4.9
208	0.4	-0.7	6.7
209	0.1	-0.3	4.1
210	0.5	0.0	7.1
MEAN	0.2	-0.1	5.3
S.D.	0.25	0.51	1.33
N	10	10	10

--: Data Unavailable

[a] Successive periods

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 2-M SEX: MALE
DOSE: 1(mg/kg)

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
221	1.0	1.4	-0.8	0.6	0.2	0.8	0.5	0.2	-0.7	0.6	0.3
222	-0.1	1.8	-1.0	0.1	0.0	1.5	0.1	0.0	0.4	0.3	1.1
223	1.0	1.4	0.2	0.6	0.6	0.8	-0.2	0.9	0.9	1.0	0.9
224	1.8	1.2	-0.7	0.7	-0.1	0.5	0.9	0.2	0.0	0.8	1.1
225	1.2	0.2	0.8	1.1	0.8	0.5	0.0	0.3	0.1	0.5	0.7
226	0.8	2.0	-0.6	0.7	0.8	1.0	0.5	0.1	0.6	1.2	-0.2
227	2.9	1.2	0.2	0.1	0.4	-0.2	0.3	0.7	-0.3	0.2	0.6
228	0.2	2.1	-0.3	0.1	0.8	-0.2	-0.1	1.0	-0.3	0.4	-0.2
229	1.5	1.3	0.1	0.3	0.6	0.4	0.6	0.3	0.4	0.1	0.6
230	1.2	1.0	-0.1	0.5	0.4	1.1	-0.3	0.1	0.6	1.0	-0.1
MEAN	1.2	1.4	-0.2	0.5	0.5	0.6	0.2	0.4	0.2	0.6	0.5
S.D.	0.83	0.55	0.56	0.33	0.33	0.54	0.39	0.36	0.50	0.38	0.51
N	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 2-M SEX: MALE
DOSE: 1(mg/kg)

ANIMAL #	DAY 84	DAY 90	TOTAL GAIN
221	0.3	0.2	4.6
222	1.1	-0.4	4.9
223	-0.2	0.5	8.4
224	0.6	-0.2	6.8
225	-0.4	0.7	6.5
226	0.4	0.3	7.6
227	0.6	0.2	6.9
228	0.9	-0.2	4.2
229	-0.5	0.3	6.0
230	-0.2	0.1	5.3
MEAN	0.3	0.2	6.1
S.D.	0.56	0.34	1.37
N	10	10	10

--: Data Unavailable

[a]Successive periods

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 3-M SEX: MALE
DOSE: 5(mg/kg)

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
241	-0.6	1.6	-1.0	1.0	0.4	0.5	0.0	0.4	0.2	0.3	0.2
242	1.3	1.5	-0.4	0.1	0.4	-0.4	0.8	-0.1	0.8	-0.4	-0.1
243	1.5	1.2	-0.5	0.6	0.4	0.3	0.8	0.1	0.9	0.5	1.0
244	1.1	0.2	0.6	0.5	0.1	1.1	0.0	0.0	0.2	-0.2	1.0
245	1.8	0.3	0.0	0.4	0.5	0.9	0.0	0.3	-0.2	1.5	-0.1
246	1.9	1.0	1.0	0.6	0.6	-0.2	-0.2	1.4	-0.2	0.8	-0.1
247	0.9	1.4	0.4	0.1	0.7	0.6	1.0	-0.4	0.0	0.4	0.2
248	1.0	0.6	0.1	0.2	0.5	1.0	-0.2	0.3	0.7	0.0	0.2
249	1.5	1.0	-0.6	0.4	0.5	0.5	0.1	0.8	0.2	0.4	0.5
250	2.1	1.2	-0.1	0.8	1.5	1.2	-1.6	1.5	1.6	-0.2	2.3
MEAN	1.3	1.0	-0.1	0.5	0.6	0.6	0.1	0.4	0.4	0.3	0.5
S.D.	0.76	0.49	0.60	0.29	0.37	0.54	0.74	0.63	0.57	0.56	0.75
N	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 3-M SEX: MALE
DOSE: 5(mg/kg)

ANIMAL #	DAY 84	DAY 90	TOTAL GAIN
241	0.2	0.6	3.8
242	0.5	0.2	4.2
243	-0.9	0.2	6.1
244	0.5	0.0	5.1
245	0.0	-0.5	4.9
246	0.3	0.1	7.0
247	0.2	1.3	6.8
248	-0.3	0.9	5.0
249	0.2	0.2	5.7
250	-0.7	0.3	9.9
MEAN	0.0	0.3	5.9
S.D.	0.48	0.50	1.76
N	10	10	10

--: Data Unavailable

[a]Successive periods

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 4-M SEX: MALE
DOSE: 25(mg/kg)

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
261	1.9	0.8	0.6	0.4	0.4	0.6	0.9	0.3	-0.9	0.7	-0.1
262	0.8	1.0	-0.1	0.2	0.6	0.2	0.6	-0.3	0.7	0.0	0.6
263	0.6	1.3	0.2	0.3	0.4	0.6	0.4	0.1	0.5	0.8	0.1
264	0.0	1.4	0.2	0.5	1.0	0.6	0.1	0.8	0.2	0.4	0.0
265	1.0	0.8	0.1	0.2	0.3	0.5	0.9	0.5	-0.8	0.7	0.3
266	0.7	0.5	0.4	0.9	-0.1	0.3	0.3	1.1	0.1	0.1	-0.6
267	-0.3	1.0	0.3	0.2	0.8	0.5	-0.1	0.2	0.7	0.0	0.3
268	1.0	1.0	-0.4	0.3	0.7	0.5	0.3	0.5	0.3	0.0	0.5
269	1.6	0.8	-0.1	0.4	0.6	0.3	0.1	-0.4	1.0	0.1	0.2
270	1.9	1.1	-0.3	0.4	1.0	0.5	0.6	0.5	0.2	0.3	0.5
MEAN	0.9	1.0	0.1	0.4	0.6	0.5	0.4	0.3	0.2	0.3	0.2
S.D.	0.74	0.26	0.31	0.21	0.34	0.14	0.34	0.46	0.62	0.32	0.36
N	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 4-M SEX: MALE
DOSE: 25(mg/kg)

ANIMAL #	DAY 84	DAY 90	TOTAL GAIN
261	0.9	0.7	7.2
262	-0.1	0.3	4.5
263	-0.4	-0.1	4.8
264	0.8	0.2	6.2
265	0.5	-0.1	4.9
266	1.0	-0.3	4.4
267	0.4	0.0	4.0
268	-0.2	0.3	4.8
269	-0.1	0.1	4.6
270	0.4	0.5	7.6
MEAN	0.3	0.2	5.3
S.D.	0.50	0.30	1.25
N	10	10	10

--: Data Unavailable

[a]Successive periods

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
211	0.8	0.8	0.9	0.6	0.4	-0.5	0.6	0.8	0.0	0.9	0.8
212	0.4	2.7	0.2	-0.1	0.4	1.9	-0.3	-0.1	0.5	1.2	0.4
213	1.2	1.3	0.2	0.7	2.1	-1.2	0.1	1.4	1.2	0.3	-0.5
214	1.6	1.4	0.2	0.7	0.3	0.0	-0.3	0.3	0.9	0.2	-0.3
215	1.7	1.2	0.2	0.7	1.1	0.8	-1.1	0.8	1.2	0.8	-0.8
216	1.5	0.9	0.4	0.8	0.6	0.7	-0.1	0.0	1.4	-0.5	0.3
217	0.5	1.9	0.7	0.4	-0.2	0.2	0.8	0.5	0.1	0.4	0.6
218	1.4	2.0	-0.4	0.7	0.7	0.4	-0.1	0.4	1.5	0.4	-0.3
219	2.3	1.2	0.6	0.4	0.2	0.7	0.0	0.3	1.0	0.0	0.6
220	0.7	1.5	1.2	0.5	0.5	0.7	0.5	0.0	-0.2	0.0	1.2
MEAN	1.2	1.5	0.4	0.5	0.6	0.4	0.0	0.4	0.8	0.4	0.2
S.D.	0.60	0.57	0.45	0.26	0.62	0.83	0.54	0.46	0.62	0.50	0.64
N	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 84	DAY 90	TOTAL GAIN
211	-0.2	-0.4	5.5
212	0.8	1.3	9.3
213	1.4	-0.2	8.0
214	0.3	0.1	5.4
215	-0.5	0.4	6.5
216	-0.1	0.4	6.3
217	-0.2	0.0	5.7
218	-1.0	1.6	7.3
219	-0.2	0.9	8.0
220	0.3	-0.3	6.6
MEAN	0.1	0.4	6.9
S.D.	0.68	0.69	1.27
N	10	10	10

--: Data Unavailable

[a]Successive periods

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 2-F SEX: FEMALE
DOSE: 1(mg/kg)

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
231	2.0	1.8	-0.5	0.4	1.1	0.7	-0.6	-0.4	3.2	0.3	-0.3
232	0.7	1.2	0.7	1.5	1.1	-0.4	-0.2	0.2	0.9	0.4	0.0
233	1.3	1.2	0.7	0.9	0.1	1.0	0.0	0.6	0.1	0.6	-0.3
234	0.3	1.6	1.2	0.9	0.0	0.5	0.8	-0.4	0.5	0.4	1.6
235	1.8	1.1	0.0	0.7	0.9	1.8	-0.5	0.3	1.6	0.3	0.5
236	1.1	0.8	0.6	1.3	0.1	0.6	0.3	0.7	-0.1	1.7	-0.6
237	0.7	1.0	1.4	0.6	-0.1	0.8	0.4	0.1	0.0	0.6	1.0
238	2.2	1.3	0.6	0.1	0.7	1.2	0.4	0.1	2.9	-0.1	0.2
239	1.7	1.0	0.6	1.2	0.3	-0.2	0.5	0.7	1.3	-0.3	1.0
240	1.8	1.1	0.8	0.9	0.5	0.7	0.0	1.3	0.4	-0.8	-0.3
MEAN	1.4	1.2	0.6	0.9	0.5	0.7	0.1	0.3	1.1	0.3	0.3
S.D.	0.64	0.30	0.54	0.42	0.46	0.63	0.45	0.52	1.18	0.66	0.72
N	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 2-F SEX: FEMALE
DOSE: 1(mg/kg)

ANIMAL #	DAY 84	DAY 90	TOTAL GAIN
231	-1.1	2.2	8.8
232	0.1	0.8	7.0
233	0.4	0.0	6.6
234	0.6	-1.0	7.0
235	0.5	2.8	11.8
236	0.1	-0.3	6.3
237	-0.3	-0.2	6.0
238	-0.9	1.6	10.3
239	1.2	-0.2	8.8
240	2.0	0.0	8.4
MEAN	0.3	0.6	8.1
S.D.	0.92	1.24	1.88
N	10	10	10

--: Data Unavailable

[a]Successive periods

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 3-F SEX: FEMALE
DOSE: 5(mg/kg)

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
251	0.9	1.6	0.8	0.2	0.5	0.5	0.4	0.1	0.2	0.3	0.6
252	1.9	0.2	1.1	0.5	0.2	0.2	0.1	1.2	0.1	0.0	0.1
253	1.4	1.0	0.6	0.7	0.7	0.5	0.1	1.0	0.2	-1.2	1.1
254	2.1	0.6	0.3	0.2	2.7	-1.1	0.3	-0.3	1.9	0.3	-0.2
255	1.8	1.1	0.4	0.4	1.0	0.5	-0.3	0.3	1.2	0.1	-0.1
256	1.2	0.8	0.9	1.4	0.0	1.0	0.3	0.7	0.3	0.4	0.0
257	0.0	1.4	1.9	-0.1	0.4	0.3	1.1	0.6	0.7	-0.6	1.4
258	1.1	1.0	0.2	1.0	-0.6	-0.7	2.2	0.5	0.9	0.2	0.0
259	1.3	1.7	0.4	0.6	0.3	1.5	0.2	0.4	0.1	2.3	-0.1
260	0.4	0.7	0.8	2.1	0.1	0.1	0.4	1.4	0.0	0.0	0.2
MEAN	1.2	1.0	0.7	0.7	0.5	0.3	0.5	0.6	0.6	0.2	0.3
S.D.	0.66	0.47	0.50	0.65	0.87	0.75	0.70	0.51	0.62	0.89	0.55
N	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

INDIVIDUAL WEIGHT GAIN (Grams) [a]

STUDY: 166 GROUP: 3-F SEX: FEMALE
DOSE: 5(mg/kg)

ANIMAL #	DAY 84	DAY 90	TOTAL GAIN
251	-0.3	0.2	6.0
252	0.6	0.2	6.4
253	1.5	-1.0	6.6
254	1.1	0.2	8.1
255	-0.2	0.5	6.7
256	1.2	0.0	8.2
257	0.6	-1.1	6.6
258	0.7	-0.1	6.4
259	-0.1	0.9	9.5
260	0.4	-0.2	6.4
MEAN	0.6	0.0	7.1
S.D.	0.61	0.62	1.12
N	10	10	10

--: Data Unavailable

[a] Successive periods

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 4-F SEX: FEMALE
DOSE: 25(mg/kg)

ANIMAL #	DAY 7[b]	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
271	1.9	0.2	1.2	0.9	-0.1	-0.2	0.0	0.8	-0.2	0.8	-0.1
272	0.8	0.4	0.4	0.8	1.0	0.1	0.1	0.5	0.9	0.5	-0.3
273	2.0	0.8	0.8	0.3	0.5	1.6	-0.1	0.5	0.0	1.1	0.7
274	1.0	0.7	1.4	0.1	0.0	0.4	1.0	0.1	0.5	0.5	2.1
275	1.9	1.7	0.5	-0.1	0.9	0.0	-0.1	0.7	0.3	0.7	0.2
276	1.1	1.1	1.0	0.7	0.6	-0.1	0.2	1.2	1.0	-0.5	-0.2
277	1.0	0.9	1.4	0.7	1.5	0.0	-0.5	0.6	1.4	0.5	0.2
278	0.9	0.9	1.5	0.3	0.1	0.7	1.0	0.4	0.9	1.5	-2.2
279	1.3	0.2	1.7	0.3	0.4	-0.3	-0.1	1.4	-0.1	-0.5	0.5
280	0.9	0.9	0.9	0.7	0.1	1.0	-0.4	0.0	0.2	0.7	0.2
MEAN	1.3	0.8	1.1	0.5	0.5	0.3	0.1	0.6	0.5	0.5	0.1
S.D.	0.47	0.45	0.43	0.33	0.51	0.61	0.51	0.44	0.54	0.63	1.06
N	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Successive periods

[b] Baseline is day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 166 GROUP: 4-F SEX: FEMALE
DOSE: 25(mg/kg)

ANIMAL #	DAY 84	DAY 90	TOTAL GAIN
271	1.2	-1.0	5.4
272	0.1	0.5	5.8
273	-0.9	1.0	8.3
274	-2.2	1.6	7.2
275	0.5	0.3	7.5
276	1.7	0.2	8.0
277	-0.3	0.7	8.1
278	0.0	1.2	7.2
279	1.7	-0.8	5.7
280	0.1	0.8	6.1
MEAN	0.2	0.5	6.9
S.D.	1.20	0.82	1.09
N	10	10	10

--: Data Unavailable

[a] Successive periods

APPENDIX 5

INDIVIDUAL FOOD CONSUMPTION DATA

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 1-M SEX: MALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
201	3.7	4.1	3.9	3.5	3.0	3.0	3.2	4.1	3.8	3.2	3.4	4.0
202	4.7	5.2	5.6	5.0	5.2	4.2	4.4	3.0	3.6	3.3	3.4	3.9
203	6.0	6.0	6.5	18.1	6.0	5.7	8.9	7.1	5.5	5.3	4.2	5.5
204	5.3	4.5	5.3	7.4	6.3	5.2	6.2	6.0	5.1	6.1	4.1	4.5
205	5.4	5.8	6.0	5.7	5.2	5.7	7.2	5.8	5.1	4.8	3.9	4.7
206	5.6	5.0	3.1	5.2	4.7	4.8	5.8	4.8	4.7	3.5	3.3	3.6
207	5.5	5.0	4.7	4.0	3.4	3.2	3.4	3.6	3.2	2.5	2.7	2.8
208	5.3	4.9	6.2	4.4	4.6	4.1	4.8	4.6	4.0	2.8	3.3	3.2
209	5.4	5.5	5.2	5.4	3.9	3.9	4.2	4.2	4.6	4.9	4.3	3.9
210	5.6	7.1	11.2	10.1	5.5	5.0	7.6	5.1	5.1	5.0	4.9	4.9
MEAN	5.3	5.3	5.8	6.9	4.8	4.5	5.6	4.8	4.5	4.1	3.8	4.1
S.D.	0.63	0.85	2.18	4.38	1.08	0.96	1.90	1.22	0.77	1.22	0.64	0.81
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 84	DAY 90
201	4.5	4.4
202	5.3	4.9
203	6.1	5.6
204	5.2	4.9
205	6.9	6.8
206	3.8	4.6
207	3.4	2.9
208	4.2	3.1
209	4.6	4.4
210	5.6	4.8
MEAN	5.0	4.6
S.D.	1.07	1.12
N	10	10

--: Data Unavailable

[a] Inclusive intervals

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 2-M SEX: MALE
DOSE: 1 (mg/kg)

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
221	4.8	4.8	10.1	8.5	4.2	4.8	4.9	4.6	4.4	3.5	4.0	3.5
222	6.0	3.9	9.1	3.8	3.6	4.0	4.9	4.0	3.0	2.1	1.2	3.7
223	5.8	4.1	4.6	5.8	3.6	3.5	3.6	3.8	3.9	3.7	3.5	4.1
224	4.0	6.7	7.2	5.1	4.4	4.9	6.4	5.0	4.6	4.4	4.4	4.9
225	5.9	7.4	7.7	5.2	5.1	4.7	7.4	4.1	3.9	3.9	4.1	4.2
226	4.9	3.8	6.4	2.5	3.8	5.5	7.4	5.9	5.1	4.5	4.2	4.4
227	3.8	4.7	10.8	5.3	4.8	4.7	5.7	4.3	4.1	3.7	3.6	3.9
228	4.3	4.4	5.5	6.1	5.0	5.5	6.1	5.5	5.4	4.3	4.1	5.6
229	5.2	11.2	7.8	4.7	6.7	4.3	11.1	5.8	5.5	5.6	5.2	5.5
230	4.8	4.8	7.6	4.1	4.3	5.0	5.8	5.6	4.5	4.7	4.1	4.7
MEAN	5.0	5.6	7.7	5.1	4.6	4.7	6.3	4.9	4.4	4.0	3.8	4.5
S.D.	0.78	2.30	1.94	1.59	0.93	0.62	2.04	0.80	0.77	0.92	1.04	0.72
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 2-M SEX: MALE
DOSE: 1(mg/kg)

ANIMAL #	DAY 84	DAY 90
221	4.3	4.0
222	3.4	3.4
223	4.3	3.9
224	5.2	5.1
225	3.5	3.6
226	4.5	4.9
227	3.9	3.6
228	4.9	4.1
229	7.1	7.4
230	4.9	5.3
MEAN	4.6	4.5
S.D.	1.06	1.21
N	10	10

--: Data Unavailable

[a]Inclusive intervals

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 3-M SEX: MALE
DOSE: 5(mg/kg)

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
241	3.8	4.1	7.1	3.3	3.5	3.5	4.0	4.0	4.2	3.3	3.4	3.4
242	4.4	6.1	5.9	3.9	3.9	3.8	5.3	4.3	4.4	4.2	3.5	4.5
243	5.2	8.1	7.5	3.6	4.2	3.7	3.3	3.9	3.8	2.8	2.2	3.4
244	6.2	9.4	9.7	5.4	5.4	6.0	6.8	6.4	4.5	4.3	3.8	5.6
245	4.9	6.5	7.6	4.3	4.4	5.8	9.0	6.7	5.7	4.7	4.5	4.6
246	5.6	4.8	4.9	3.8	3.6	4.7	4.9	5.2	4.6	4.1	3.7	4.8
247	6.9	8.0	10.2	4.2	4.8	4.7	5.5	5.1	4.6	4.0	4.1	4.3
248	5.0	6.5	5.3	3.9	4.3	3.8	4.6	3.9	4.1	3.7	3.6	4.1
249	4.1	4.6	6.6	3.9	4.4	4.3	4.7	5.4	5.8	4.4	4.3	4.8
250	4.9	3.6	5.3	3.6	4.1	4.5	5.4	4.4	4.1	3.5	3.7	3.8
MEAN	5.1	6.2	7.0	4.0	4.3	4.5	5.4	4.9	4.6	3.9	3.7	4.3
S.D.	0.94	1.91	1.82	0.57	0.56	0.86	1.59	1.02	0.67	0.57	0.63	0.68
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams) [a]

STUDY: 166 GROUP: 3-M SEX: MALE
DOSE: 5(mg/kg)

ANIMAL #	DAY 84	DAY 90
241	3.3	3.1
242	5.2	4.6
243	3.6	3.2
244	6.6	5.5
245	4.8	4.8
246	4.9	4.4
247	4.0	4.7
248	4.1	4.3
249	4.3	4.4
250	3.6	4.5
MEAN	4.4	4.4
S.D.	0.98	0.72
N	10	10

--: Data Unavailable

[a] Inclusive intervals

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 4-M SEX: MALE
DOSE: 25(mg/kg)

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
261	5.5	3.6	4.7	3.9	3.8	3.9	3.7	4.6	4.0	3.6	3.7	3.8
262	5.0	3.0	4.2	3.5	4.0	4.1	4.1	4.3	3.9	3.8	4.0	3.9
263	4.5	4.5	5.4	3.7	4.3	4.7	3.9	4.3	3.9	3.5	3.7	3.5
264	5.0	4.4	4.0	4.2	3.9	4.9	4.3	4.6	3.6	3.7	3.2	3.9
265	5.0	3.4	4.5	4.3	3.9	4.1	4.2	4.2	4.0	3.6	3.6	3.6
266	5.7	5.8	10.4	4.8	4.7	5.1	5.7	6.0	4.7	3.9	4.2	5.1
267	0.5	8.3	10.4	4.8	4.7	4.6	6.0	5.1	4.2	3.9	4.0	4.2
268	6.3	4.9	8.0	4.2	4.3	4.0	4.9	4.3	4.1	3.4	3.5	3.7
269	7.5	3.7	13.8	5.6	5.2	5.7	7.6	4.6	4.6	4.7	5.2	5.1
270	4.9	5.5	8.3	4.5	3.8	4.3	6.2	5.1	4.4	2.3	2.8	5.3
MEAN	5.0	4.7	7.4	4.4	4.3	4.5	5.1	4.7	4.1	3.6	3.8	4.2
S.D.	1.80	1.56	3.36	0.61	0.47	0.57	1.27	0.55	0.34	0.59	0.64	0.69
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 4-M SEX: MALE
DOSE: 25(mg/kg)

ANIMAL #	DAY 84	DAY 90
261	4.7	5.7
262	4.1	3.9
263	3.8	4.9
264	4.1	3.9
265	3.6	3.7
266	5.7	4.6
267	4.3	4.8
268	4.5	4.9
269	6.0	5.1
270	3.3	5.9
MEAN	4.4	4.7
S.D.	0.87	0.74
N	10	10

--: Data Unavailable

[a]Inclusive intervals

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 0 [b]	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
211	5.0	6.7	16.5	9.2	7.1	6.1	8.3	6.6	6.0	7.0	4.6	7.5
212	4.7	7.9	16.1	7.5	6.5	6.4	9.9	7.3	5.5	6.4	4.6	4.9
213	4.3	3.8	5.1	8.8	4.8	4.8	5.9	5.0	4.9	5.4	5.1	5.6
214	5.4	9.7	13.3	13.0	8.8	7.9	8.8	7.0	7.1	6.9	5.0	6.0
215	5.5	7.8	12.6	14.1	10.9	7.7	14.8	7.5	5.7	8.7	6.6	6.0
216	4.7	9.2	16.1	14.8	8.1	5.3	11.1	7.3	5.0	6.1	4.3	3.9
217	5.1	9.4	11.5	12.1	6.1	6.6	8.9	6.3	5.6	6.9	5.7	5.7
218	7.0	8.1	12.1	14.6	6.9	6.0	9.8	7.2	6.1	7.1	5.3	5.8
219	5.0	9.7	10.8	12.7	5.9	4.7	7.5	5.6	5.2	5.1	4.4	6.2
220	10.7	6.8	9.5	9.1	6.5	5.4	5.8	5.5	4.6	4.8	4.3	5.1
MEAN	5.7	7.9	12.4	11.6	7.2	6.1	9.1	6.5	5.6	6.4	5.0	5.7
S.D.	1.89	1.82	3.50	2.70	1.73	1.10	2.63	0.89	0.72	1.15	0.73	0.94
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 84	DAY 90
211	7.9	6.7
212	7.5	6.6
213	6.7	6.1
214	7.7	7.0
215	8.6	6.8
216	5.3	6.7
217	6.6	5.3
218	6.6	5.9
219	6.1	5.3
220	5.0	4.8
MEAN	6.8	6.1
S.D.	1.15	0.77
N	10	10

--: Data Unavailable

[a]Inclusive intervals

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 2-F SEX: FEMALE
DOSE: 1(mg/kg)

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
231	5.3	7.5	12.6	7.6	5.9	4.8	8.1	6.5	5.2	5.9	4.3	5.6
232	3.6	2.5	4.1	5.5	4.3	4.5	5.8	5.2	4.7	4.9	3.7	5.1
233	7.6	9.5	10.8	7.4	6.7	6.5	8.8	6.8	5.8	5.5	4.3	5.8
234	4.8	5.8	6.9	7.0	5.6	5.3	8.2	6.4	5.2	5.1	3.7	5.5
235	4.9	6.8	10.1	6.7	5.0	6.0	8.9	6.6	8.3	6.0	4.5	6.8
236	5.5	8.2	12.1	7.8	6.0	5.7	12.8	6.1	7.4	4.8	5.2	5.9
237	6.0	9.8	8.8	7.2	6.0	6.4	9.7	6.8	5.7	5.9	4.8	6.6
238	4.3	6.9	9.4	5.2	5.5	5.3	9.8	6.9	5.9	5.9	4.4	6.2
239	4.5	5.3	8.0	4.2	4.0	4.2	8.1	4.3	3.9	3.9	2.7	4.8
240	4.0	7.8	5.0	3.9	4.7	5.4	7.2	6.8	6.9	5.4	4.1	6.3
MEAN	5.1	7.0	8.8	6.3	5.4	5.4	8.7	6.2	5.9	5.3	4.2	5.9
S.D.	1.15	2.14	2.83	1.44	0.85	0.77	1.85	0.85	1.31	0.67	0.69	0.64
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams) [a]

STUDY: 166 GROUP: 2-F SEX: FEMALE
DOSE: 1(mg/kg)

ANIMAL #	DAY 84	DAY 90
231	6.3	6.9
232	6.6	5.6
233	6.2	4.9
234	6.4	6.3
235	6.1	6.3
236	5.9	5.3
237	6.5	5.2
238	4.9	4.4
239	5.2	4.6
240	7.0	6.4
MEAN	6.1	5.6
S.D.	0.64	0.85
N	10	10

--: Data Unavailable

[a] Inclusive intervals

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 3-F SEX: FEMALE
DOSE: 5(mg/kg)

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
251	6.3	14.2	14.0	6.6	6.2	6.8	9.9	6.5	7.4	5.4	4.2	6.9
252	3.6	10.4	14.6	3.9	4.6	4.6	7.8	5.2	7.2	4.7	3.3	4.7
253	4.8	5.7	8.9	4.2	4.1	4.4	7.3	5.7	5.1	4.8	3.7	5.0
254	4.7	8.4	11.4	6.4	4.9	5.7	10.1	7.1	5.9	5.6	3.3	6.1
255	4.1	10.1	13.4	5.3	5.7	5.7	7.9	5.4	4.4	4.5	4.1	4.8
256	6.9	8.6	12.9	3.8	5.5	3.9	6.7	6.9	5.7	5.2	3.4	5.8
257	4.7	12.3	7.9	5.1	4.6	5.8	7.1	6.5	4.5	5.8	5.5	5.8
258	3.7	8.3	9.2	5.5	5.2	4.6	8.1	6.1	5.7	4.9	4.1	4.3
259	6.0	8.2	15.1	7.3	6.3	6.4	11.1	7.0	6.1	5.9	6.3	6.8
260	4.6	4.5	7.8	4.5	4.6	5.4	7.7	6.1	5.0	4.7	4.0	5.2
MEAN	4.9	9.1	11.5	5.3	5.2	5.3	8.4	6.3	5.7	5.2	4.2	5.5
S.D.	1.11	2.86	2.85	1.20	0.74	0.93	1.47	0.67	1.02	0.50	0.98	0.89
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 3-F SEX: FEMALE
DOSE: 5(mg/kg)

ANIMAL #	DAY 84	DAY 90
251	6.1	6.8
252	3.3	5.6
253	4.3	4.3
254	5.7	6.0
255	4.8	5.5
256	5.3	5.8
257	5.8	5.0
258	5.0	4.4
259	6.9	7.6
260	5.5	6.2
MEAN	5.3	5.7
S.D.	1.00	1.02
N	10	10

--: Data Unavailable

[a]Inclusive intervals

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 4-F SEX: FEMALE
DOSE: 25(mg/kg)

ANIMAL #	DAY 0[b]	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77
271	5.3	5.8	7.7	7.0	5.8	6.0	7.6	5.9	5.4	4.2	4.5	5.7
272	6.0	8.4	15.1	7.5	5.5	6.4	12.4	7.4	6.9	5.6	4.8	5.3
273	6.0	9.6	5.7	7.7	6.4	6.7	10.5	8.1	7.9	6.0	6.0	7.1
274	4.6	7.1	7.1	4.4	3.2	4.5	8.3	5.2	4.6	3.3	4.2	3.2
275	5.4	6.9	12.4	5.4	5.1	8.7	8.2	4.8	5.0	4.3	3.9	4.0
276	6.2	14.2	11.5	7.8	6.8	10.3	11.8	7.6	10.9	7.0	5.7	7.4
277	6.1	5.9	9.0	7.0	5.4	9.0	9.0	5.9	5.8	4.7	4.5	5.2
278	6.1	7.5	9.1	7.9	5.2	9.0	15.6	5.4	5.7	4.8	5.1	5.0
279	6.3	10.6	12.3	6.2	4.5	9.8	10.2	5.8	6.5	3.7	4.8	4.3
280	5.9	7.5	9.4	6.8	5.6	13.2	12.1	5.8	6.0	4.7	4.1	4.7
MEAN	5.8	8.4	9.9	6.8	5.4	8.4	10.6	6.2	6.5	4.8	4.8	5.2
S.D.	0.53	2.55	2.86	1.14	1.00	2.52	2.47	1.11	1.82	1.11	0.68	1.30
N	10	10	10	10	10	10	10	10	10	10	10	10

--: Data Unavailable

[a] Inclusive intervals

[b] Food in on day -6

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 166 GROUP: 4-F SEX: FEMALE
DOSE: 25(mg/kg)

ANIMAL #	DAY 84	DAY 90
271	6.8	5.6
272	4.2	5.0
273	6.2	6.8
274	2.9	3.4
275	4.5	4.4
276	7.6	8.3
277	5.5	6.3
278	5.7	7.1
279	6.1	6.2
280	6.6	6.0
MEAN	5.6	5.9
S.D.	1.40	1.40
N	10	10

--: Data Unavailable

[a]Inclusive intervals

APPENDIX 6

INDIVIDUAL CLINICAL CHEMISTRY DATA

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Clinical Chemistry Test Directory

STUDY: 166

NO.	ABBR. / UNITS	DESCRIPTION / PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT--- MALE	FEMALE	---UPPER LIMIT--- MALE	FEMALE
1.	ALT	Alanine Aminotransferase							
	IU/L	Integer	NO			30	30	100	100
2.	ALKP	Alkaline Phosphatase							
	IU/L	Integer	NO			100	150	200	250
3.	CHOL	Cholesterol							
	mg/dL	Integer	NO			60	60	125	125
4.	TRIG	Triglycerides							
	mg/dL	Integer	NO			150	150	350	350
5.	BUN	Blood Urea Nitrogen							
	mg/dL	0.0	NO			25.0	25.0	37.0	37.0
6.	GLU	Glucose							
	mg/dL	Integer	NO			100	100	200	200
7.	SDH	Sorbitol Dehydrogenase							
	IU/L	0.0	NO			10	10	30	30
8.	TP	Total Protein							
	g/dL	0.0	NO			6.0	6.0	9.5	9.5
9.	ALB	Albumin							
	g/dL	0.0	NO			3.4	3.4	5.6	5.6
10.	GLOB	Globulin							
	g/dL	0.0	Operand A - Operand B	TP	ALB	2.5	2.5	5	5
11.	A/G	A/G Ratio							
	-	0.00	Operand A / Operand B	ALB	GLOB	0.75	.75	1.5	1.5
12.	TBA	Total Bile Acids							
	umol/L	0.0	NO			25.0	75.0	25.0	75.0
13.	IP	Inorganic Phosphorus							
	mg/dL	0.0	NO			5.5	5.5	11.0	11.0
14.	TSH	Thyriod Stimulating Hormone							
	ng/ml	0.00	NO			250	250	350	350

(END OF REPORT)

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: MALE

Animal ID	ALT IU/L	SDH IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBA umol/L	ALKP IU/L
GROUP: 1-M:0 mg/kg/day								
201	--	--	5.7	3.1	2.6	1.19	24.5	--
202	30	19.1	7.8	4.3	3.5	1.23	16.3	91
203	199	--	--	--	--	--	--	87
204	53	16.5	--	--	--	--	--	83
205	--	7.6	--	--	--	--	--	--
206	--	--	6.0	3.3	2.7	1.22	34.2	--
207	--	--	--	--	--	--	--	--
208	165	11.9	--	--	--	--	--	51
209	35	20.9	6.4	3.7	2.7	1.37	29.4	79
210	--	--	9.6	4.8	4.8	1.00	60.8	--
MEAN	96	15.2	7.1	3.8	3.3	1.20	33.0	78
SD	79.5	5.43	1.61	0.71	0.93	0.133	16.87	15.8
N	5	5	5	5	5	5	5	5
GROUP: 2-M:1 mg/kg/day								
221	--	--	--	--	--	--	--	--
222	115	--	--	--	--	--	--	101
223	95	--	--	--	--	--	--	99
224	127	15.8	10.4	5.6	4.8	1.17	36.4	92
225	--	1.1	7.3	4.1	3.2	1.28	33.7	--
226	104	1.5	--	--	--	--	--	99
227	--	--	9.2	6.0	3.2	1.88	63.6	--
228	--	1.6	9.3	4.8	4.5	1.07	54.3	--
229	--	--	--	--	--	--	--	--
230	103	18.6	7.6	6.4	1.2	5.33	56.8	86
MEAN	109	7.7	8.8	5.4	3.4	2.15	49.0	95
SD	12.4	8.71	1.29	0.93	1.42	1.808	13.18	6.3
N	5	5	5	5	5	5	5	5

(--) - Data Unavailable

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: MALE

Animal ID	ALT IU/L	SDH IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBA umol/L	ALKP IU/L
GROUP: 3-M:5 mg/kg/day								
241	30	28.8	--	--	--	--	--	84
242	--	--	5.8	3.9	1.9	2.05	22.2	--
243	--	--	--	--	--	--	--	--
244	30	8.8	7.6	4.3	3.3	1.30	22.1	103
245	--	--	6.1	3.3	2.8	1.18	30.5	--
246	72	25.6	6.7	2.4	4.3	0.56	58.4	70
247	360	4.5	--	--	--	--	--	92
248	--	--	--	--	--	--	--	--
249	--	--	--	--	--	--	--	--
250	108	20.7	7.0	3.8	3.2	1.19	23.5	82
MEAN	120	17.7	6.6	3.5	3.1	1.26	31.3	86
SD	138.1	10.58	0.72	0.73	0.87	0.531	15.52	12.3
N	5	5	5	5	5	5	5	5
GROUP: 4-M:25 mg/kg/day								
261	338	8.9	--	--	--	--	--	116
262	--	--	5.6	2.9	2.7	1.07	25.2	--
263	49	13.6	7.0	--	--	--	--	96
264	--	--	--	3.3	--	--	25.7	--
265	--	--	--	--	--	--	--	--
266	60	27.1	6.1	3.3	2.8	1.18	41.6	90
267	--	--	5.6	3.1	2.5	1.24	45.9	--
268	225	16.3	--	--	--	--	--	95
269	189	6.2	--	--	--	--	--	88
270	--	--	5.4	2.9	2.5	1.16	59.5	--
MEAN	172	14.4	5.9	3.1	2.6	1.16	39.6	97
SD	120.8	8.11	0.65	0.20	0.15	0.070	14.49	11.1
N	5	5	5	5	4	4	5	5

(--) - Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: MALE

Animal ID	CHOL mg/dL	TRIG mg/dL	BUN mg/dL	IP mg/dL	GLU mg/dL	TSH ug/ml
GROUP: 1-M:0 mg/kg/day						
201	--	--	--	11.3	--	--
202	89	80	19.3	10.0	171	0.02
203	106	--	--	--	184	0.20
204	92	166	25.0	--	243	0.12
205	--	--	--	--	--	--
206	--	134	24.4	14.0	--	--
207	--	--	--	--	--	--
208	96	98	21.8	--	189	0.02
209	72	85	21.0	6.8	214	0.07
210	--	--	--	--	--	--
MEAN	91	113	22.3	10.5	200	0.09
SD	12.4	36.6	2.38	2.99	28.6	0.076
N	5	5	5	4	5	5
GROUP: 2-M:1 mg/kg/day						
221	--	203	--	--	--	--
222	108	176	25.8	--	175	0.07
223	--	--	--	--	161	0.07
224	96	143	24.3	--	147	0.13
225	--	--	--	13.6	--	--
226	115	164	26.0	--	163	0.01
227	--	--	--	--	--	--
228	107	--	42.1	21.6	--	--
229	--	--	--	--	--	--
230	100	118	21.9	--	203	0.13
MEAN	105	161	28.0	17.6	170	0.08
SD	7.4	32.3	8.04	5.66	21.1	0.050
N	5	5	5	2	5	5

(--) - Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: MALE

Animal ID	CHOL mg/dL	TRIG mg/dL	BUN mg/dL	IP mg/dL	GLU mg/dL	TSH ug/ml
GROUP: 3-M:5 mg/kg/day						
241	96	112	25.4	--	169	0.00
242	--	--	--	17.6	--	--
243	--	--	--	--	--	--
244	90	83	25.6	10.0	167	0.03
245	--	158	32.5	17.0	--	--
246	107	148	23.5	--	196	0.00
247	100	--	--	--	216	0.72
248	--	--	--	--	--	--
249	--	--	--	--	--	--
250	98	150	21.2	11.2	231	0.11
MEAN	98	130	25.6	14.0	196	0.17
SD	6.2	31.8	4.23	3.91	28.3	0.310
N	5	5	5	4	5	5
GROUP: 4-M:25 mg/kg/day						
261	122	145	28.8	--	170	0.11
262	--	--	--	14.0	--	--
263	106	165	26.8	--	200	0.17
264	--	--	--	10.0	--	--
265	--	--	--	--	--	--
266	78	104	26.7	--	171	0.00
267	--	--	--	21.4	--	--
268	85	104	24.6	--	293	0.39
269	114	126	26.9	--	151	0.15
270	--	--	--	19.4	--	--
MEAN	101	129	26.8	16.2	197	0.16
SD	18.8	26.5	1.49	5.18	56.4	0.142
N	5	5	5	4	5	5

(--) - Data Unavailable

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: FEMALE

Animal ID	ALT IU/L	SDH IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBA umol/L	ALKP IU/L
GROUP: 1-F:0 mg/kg/day								
211	--	11.3	--	--	--	--	--	93
212	--	22.4	6.9	--	--	--	--	132
213	35	--	--	3.1	--	--	31.5	--
214	26	29.8	6.3	3.5	2.8	1.25	27.1	112
215	28	26.8	7.1	4.1	3.0	1.37	--	124
216	33	28.0	6.5	3.6	2.9	1.24	26.2	128
217	--	--	--	--	--	--	--	--
218	41	--	6.1	3.5	2.6	1.35	31.5	--
219	--	--	--	--	--	--	24.9	--
220	--	--	--	--	--	--	--	--
MEAN	33	23.7	6.6	3.6	2.8	1.30	28.2	118
SD	5.9	7.43	0.41	0.36	0.17	0.067	3.08	15.8
N	5	5	5	5	4	4	5	5
GROUP: 2-F:1 mg/kg/day								
231	31	33.4	6.7	3.6	3.1	1.16	26.5	141
232	28	28.0	6.5	3.7	2.8	1.32	24.2	128
233	--	--	--	--	--	--	--	--
234	--	--	--	--	--	--	--	--
235	27	16.0	7.0	3.7	3.3	1.12	38.1	96
236	--	--	--	--	--	--	--	--
237	--	--	--	--	--	--	--	--
238	--	--	--	--	--	--	--	--
239	41	23.3	6.5	3.8	2.7	1.41	25.2	115
240	81	11.6	6.0	3.1	2.9	1.07	35.0	116
MEAN	42	22.5	6.5	3.6	3.0	1.22	29.8	119
SD	22.7	8.81	0.36	0.28	0.24	0.143	6.31	16.7
N	5	5	5	5	5	5	5	5

(--) - Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: FEMALE

Animal ID	ALT IU/L	SDH IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBA umol/L	ALKP IU/L
GROUP: 3-F:5 mg/kg/day								
251	--	--	--	--	--	--	--	--
252	25	23.7	--	--	--	--	--	123
253	--	--	5.0	2.7	2.3	1.17	25.2	--
254	--	--	--	--	--	--	--	--
255	82	22.4	--	--	--	--	--	132
256	24	24.2	6.5	3.5	3.0	1.17	25.6	125
257	--	--	--	--	--	--	--	--
258	43	30.1	6.5	3.6	2.9	1.24	28.6	148
259	43	33.2	6.2	3.2	3.0	1.07	27.3	100
260	--	--	5.3	2.9	2.4	1.21	26.9	--
MEAN	43	26.7	5.9	3.2	2.7	1.17	26.7	126
SD	23.5	4.68	0.70	0.38	0.34	0.064	1.37	17.4
N	5	5	5	5	5	5	5	5
GROUP: 4-F:25 mg/kg/day								
271	34	32.2	5.8	2.8	3.0	0.93	--	137
272	--	--	--	--	--	--	--	--
273	--	--	5.4	3.0	2.4	1.25	19.5	--
274	--	--	--	--	--	--	--	--
275	74	23.1	--	--	--	--	--	121
276	32	30.8	6.1	3.2	2.9	1.10	28.6	113
277	--	--	--	--	--	--	--	--
278	58	18.9	7.2	3.8	3.4	1.12	36.0	136
279	--	--	--	--	--	--	19.4	--
280	66	24.4	5.9	3.2	2.7	1.19	34.2	124
MEAN	53	25.9	6.1	3.2	2.9	1.12	27.5	126
SD	19.0	5.54	0.68	0.37	0.37	0.121	7.87	10.2
N	5	5	5	5	5	5	5	5

(--) - Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: FEMALE

Animal ID	CHOL mg/dL	TRIG mg/dL	BUN mg/dL	IP mg/dL	GLU mg/dL	TSH ug/ml
GROUP: 1-F:0 mg/kg/day						
211	79	188	--	--	153	0.11
212	93	151	--	--	165	0.10
213	--	--	35.7	8.9	--	--
214	81	105	20.1	8.9	187	0.01
215	96	157	18.6	--	182	0.13
216	81	77	18.7	9.1	205	0.05
217	--	--	--	--	--	--
218	--	--	--	11.3	--	--
219	--	--	--	9.7	--	--
220	--	--	31.6	--	--	--
MEAN	86	136	24.9	9.6	178	0.08
SD	7.9	44.2	8.10	1.02	20.1	0.049
N	5	5	5	5	5	5
GROUP: 2-F:1 mg/kg/day						
231	94	135	20.6	10.3	198	0.00
232	87	87	23.5	8.2	192	0.06
233	--	--	--	--	--	--
234	--	--	--	--	--	--
235	83	110	19.7	10.9	228	0.03
236	--	--	--	--	--	--
237	--	--	--	10.1	--	--
238	--	--	--	--	--	--
239	98	189	21.4	--	189	0.06
240	80	121	29.1	10.4	208	0.04
MEAN	88	128	22.9	10.0	203	0.04
SD	7.5	38.2	3.76	1.04	15.7	0.025
N	5	5	5	5	5	5

(--) - Data Unavailable

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: Week 14

STUDY ID: 166
STUDY NO: 166

SEX: FEMALE

Animal ID	CHOL mg/dL	TRIG mg/dL	BUN mg/dL	IP mg/dL	GLU mg/dL	TSH ug/ml
GROUP: 3-F:5 mg/kg/day						
251	--	--	--	8.0	--	--
252	77	116	23.5	--	167	0.01
253	--	--	--	8.0	--	--
254	--	--	--	--	--	--
255	80	156	23.4	--	209	0.03
256	96	146	25.5	11.1	185	0.02
257	--	--	--	--	--	--
258	89	181	27.1	--	176	0.08
259	93	204	28.1	10.7	163	0.03
260	--	--	--	8.6	--	--
MEAN	87	161	25.5	9.3	180	0.03
SD	8.2	33.6	2.11	1.51	18.3	0.027
N	5	5	5	5	5	5
GROUP: 4-F:25 mg/kg/day						
271	93	155	26.4	--	204	0.09
272	--	--	--	9.8	--	--
273	--	--	--	8.9	--	--
274	--	--	--	--	--	--
275	86	109	24.4	--	286	0.10
276	91	160	27.6	10.0	186	0.01
277	--	--	--	--	--	--
278	107	137	22.1	--	199	0.06
279	--	--	--	8.0	--	--
280	79	114	28.1	10.0	181	0.04
MEAN	91	135	25.7	9.3	211	0.06
SD	10.4	23.2	2.48	0.88	42.8	0.037
N	5	5	5	5	5	5

(--) - Data Unavailable

APPENDIX 7

TSH MEASUREMENTS AND METHODOLOGY

DRAFT

ANALYTICS INCORPORATED
200 Girard Street, Suite 200, Gaithersburg, MD 20877
301-921-0168 800-237-2815

Client: UNIV. OF ILLINOIS AT CHICAGO
DEPT. OF PHARMACOLOGY MIL 868
1940 WEST TAYLOR STREET
CHICAGO, IL 60612
(312) 996-5543
Attention: DR BARRY LEVINE

Date Collected: 05/18/95-05/19/95
Date Received: 05/24/95
Date Reported: 06/29/95

Client No. 1063 Study: UIC/TRL 166 Species: MOUSE

Accession No.	Animal No.	Gp	Sex	Age	TSH, MO UG/ML
N 0023255	211	1	F	21W	0.11
N 0023256	212	1	F	21W	0.10
N 0023265	216	1	F	21W	0.05
N 0023267	214	1	F	21W	0.01
N 0023273	215	1	F	21W	0.13
	Mean				.08
	S.D.				.049
Group 1					
N 0023235	203	1	M	21W	0.20
N 0023237	204	1	M	21W	0.12
N 0023240	208	1	M	21W	0.02
N 0023248	202	1	M	21W	0.02
N 0023251	209	1	M	21W	0.07
	Mean				.086
	S.D.				.076
Group 1					
N 0023260	240	2	F	21W	0.04
N 0023264	235	2	F	21W	0.03
N 0023266	232	2	F	21W	0.06
Reference Range					0 - 0

DRAFT

*Corrected Report

ANALYTICS INCORPORATED
200 Girard Street, Suite 200, Gaithersburg, MD 20877
301-921-0168 800-237-2815

Client: UNIV. OF ILLINOIS AT CHICAGO
DEPT. OF PHARMACOLOGY MIL 868
1940 WEST TAYLOR STREET
CHICAGO, IL 60612
(312) 996-5543
Attention: DR BARRY LEVINE

Date Collected: 05/18/95-05/19/95
Date Received: 05/24/95
Date Reported: 06/29/95

Client No. 1063 Study: UIC/TRL 166 Species: MOUSE

Accession No.	Animal No.	Gp	Sex	Age	TSH, MO UG/ML
N0023268	239	2	F	21W	0.06
N 0023269	231	2	F	21W	0.00
	Mean				.038
	S.D.				.025
Group 2					
N0023236	223	2	M	21W	0.07
N0023238	222	2	M	21W	0.07
N 0023239	226	2	M	21W	0.01
N0023246	230	2	M	21W	0.13
N0023249	224	2	M	21W	0.13
	Mean				.082
	S.D.				.05
Group 2					
N 0023258	258	3	F	21W	0.08
N0023259	256	3	F	21W	0.02
N0023263	259	3	F	21W	0.03
N 0023271	255	3	F	21W	0.03
N 0023272	252	3	F	21W	0.01
	Mean				.034
	S.D.				.027
Group 3					
Reference Range					0 - 0

*The animal number represented by accession number N0023249 has been corrected from original report. No other changes, including analytic values, have been made.

DRAFT

ANILYTICS INCORPORATED
200 Girard Street, Suite 200, Gaithersburg, MD 20877
301-921-0168 800-237-2815

Client: UNIV. OF ILLINOIS AT CHICAGO
DEPT. OF PHARMACOLOGY MIL 868
1940 WEST TAYLOR STREET
CHICAGO, IL 60612
(312) 996-5543
Attention: DR BARRY LEVINE

Date Collected: 05/18/95-05/19/95
Date Received: 05/24/95
Date Reported: 06/29/95

Client No. 1063 Study: UIC/TRL 166 Species: MOUSE

Accession No.	Animal No.	Gp	Sex	Age	TSH, MO UG/ML
N 0023241	247	3	M	21W	0.72
N 0023245	244	3	M	21W	0.03
N 0023247	250	3	M	21W	0.11
N 0023250	246	3	M	21W	0.00
N 0023253	241	3	M	21W	0.00
	Mean				.172
	S.D.				.31
Group 3					
N 0023257	280	4	F	21W	0.04
N 0023261	278	4	F	21W	0.06
N 0023262	271	4	F	21W	0.09
N 0023270	276	4	F	21W	0.01
N 0023274	275	4	F	21W	0.10
	Mean				.06
	S.D.				.037
Group 4					
N 0023242	263	4	M	21W	0.17
N 0023243	269	4	M	21W	0.15
N 0023244	261	4	M	21W	0.11
Reference Range					0 - 0

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Date Collected: 05/18/95-05/19/95
Date Received: 05/24/95

Date Reported: 06/29/95

Client No. 1063 Study: UIC/TRL 166 Species: MOUSE

Accession No.	Animal No.	Gp	Sex	Age	TSH, MO UG/ML
N 0023252	268	4	M	21W	0.39
N 0023254	266	4	M	21W	0.00
	Mean				.164
	S.D.				.142

Group 4

Reference Range 0 - 0

Approved [signature] Date 6/29/95

[signature] 7/9/95

DRAFT

ANALYTICS INCORPORATED
200 Girard Street, Suite 200, Gaithersburg, MD 20877
301-921-0168 800-237-2815

QA INSPECTION STATEMENT

The reports listed below were reviewed for compliance with the FDA Good Laboratory Practices and with the EPA Good Laboratory Practices. The final report and all associated raw data were reviewed for accuracy and consistency and the findings were reported to management.

The methods used were the methods described and the report accurately reflects the data. Therefore, these studies were done in compliance with the FDA and the EPA Good Laboratory Practices.

Frank Newman

Frank Newman
QA Auditor

SPONSOR: UN OF ILLINOIS AT CHICAGO STUDY: UIC/TRL 166

REPORT TYPE:	AUDIT DATE:	REPORT TO MGMT:	AUDIT #:
TSH	6-9-95	6-12-95	95-286

7-15-9

ANALYTICS INCORPORATED
200 Girard Street, Suite 200, Gaithersburg, MD 20877
301-921-0168 800-237-2815

DRAFT

Summary of Mouse TSH SOP

Mouse TSH and Rat TSH show partial cross reactivity. An assay for mouse TSH can be performed by a hybrid assay which uses antibody to rat TSH, radio-iodinated rat TSH, and mouse TSH standards.

Reagents are obtained from Albert Parlow, Pituitary Hormones and Antisera Center, Harbor UCLA Medical Center, Torrance CA.

Rat TSH antigen for iodination is NIDDK-rTSH-I-8 (AFP-8334B), radioiodinated by Corning-Hazleton, lot #95-0326.
Antibody is Rabbit anti-Rat TSH-S-5 (C21381)
Standard is Mouse TSH/LH reference preparation AFP98991

Pipette 50 ul of each serum, QC sample, or standard into tube. Add 50 ul of antibody. Add 50 ul. of radioiodinated rat TSH. Add 100 ul of buffer. Vortex all tubes gently, cover with parafilm, incubate at room temperature for 15-24 hours. Add 250 ul goat anti-rabbit precipitating reagent to each tube. Vortex all tubes gently and incubate 1 hour at room temperature. Centrifuge 2500-2800 rpm in refrigerated centrifuge. Aspirate supernatant. Count each tube for 1 min. in gamma counter. Graph the standard curve using log-logit parameters with B0 as 100. Read controls and unknowns from standard curve.

If adequate specimen is available, the assay is performed in duplicate.

ANALYTICS INCORPORATED
360 Christopher Avenue
Gaithersburg, MD 20879

DRAFT

Edition: 1
Effective Date: 1/2/91
Responsibility: All

STANDARD OPERATING PROCEDURE

RAT/MOUSE THYROID STIMULATING HORMONE (TSH)

SUMMARY and PRINCIPLE

The main functions of the thyroid gland are trapping of iodine and synthesis, storage, and release of thyroid hormones. These activities are under the control of the thyrotropic or the thyroid-stimulating hormone (TSH).

Rat/Mouse TSH is a species specific hormone and therefore testing is performed by utilizing appropriate species specific reagents obtained through the Pituitary Hormones and Antisera Center.

REAGENTS REQUIRED

1. PBS with 1% bovine serum albumin (BSA)
2. PBS with 1% BSA and 0.5% normal rabbit serum (NRS)
3. (125)I RAT TSH antigen
4. RAT TSH antibody (made in rabbit)
5. RAT TSH reference standard/MOUSE TSH reference standard
6. GOAT anti RABBIT precipitating reagent

(125)I RAT TSH PREPARATION: Make appropriate dilution (125)I RAT TSH in PBS/BSA/NRS to obtain approxomately 25,000 counts per 200 ul. (For mouse assay, 25,000 counts per 50 ul

RAT TSH ANTIBODY PREPARATION: Dilute antibody in PBS/BSA/NRS. Adjust dilution appropriately to achieve a dilution yielding a maximum binding in the range of 25-35%.

STANDARD CURVE PREPARATION: Dilute the RAT TSH reference standard in PBS/BSA/NRS appropriately to obtain a standard curve in the approximate range of 50 to 0.39ng/ml. Dilute MOUSE TSH reference standard in PBS/BSA/NRS appropriately to obtain a standard curve in the approximate range of 14 to 0.4 ug/ml.

SPECIMEN REQUIREMENT: Frozen Serum

1/2/91 FAN 3-20-91

RAT/MOUSE TSH ASSAY

DRAFT

1. As a rule, run each specimen in duplicate.
2. Label tubes for total count (TC), nonspecific binding (NSB), maximum binding (B0), standard curve, controls, and unknown specimens.
3. Rat Standard Curve: Use 100ul of each standard. Add 100ul of buffer to all tubes. Add 200ul of buffer to NSB and B0 tubes.
   Mouse Standard Curve: Use 50ul of each standard. Add 50ul of buffer to NSB and B0 tubes.
4. Rat Specimens: Pipet 200ul of QC samples and unknowns.
   Mouse Specimens: Pipet 50ul of QC samples and unknowns.
5. Antibody: Pipet 200 ul of antibody into all tubes of rat assay except NSB. Add 200ul buffer to NSB tubes.
   Antibody: Pipet 50ul of antibody into all tubes of mouse assay except NSB. Add 50ul of buffer to NSB tubes.
6. (125)I Rat TSH: Add 200ul to all tubes of rat assay.
   Add 50ul to all tubes of mouse assay.
7. Final Reaction Volume: Add 400ul of buffer to rat assay tubes (final volume 1ml). Add 100ul of buffer to mouse assay tubes (final volume 250ul).
8. Vortex all tubes gently, cover with parafilm, and incubate 15-24 hours at room temperature.
9. Second Antibody (Goat Anti Rabbit Precipitating Reagent):
   Add 1ml to all rat assay tubes.
   Add 250ul to all mouse assay tubes.
10. Vortex all tubes gently and incubate 1 hour at room temperature.
11. Centrfuge at 2500-2800 rpm in a refrigerated centrifuge for a minimum of 30 minutes.
11. Carefully aspirate supernatant.
12. Count each tube for 1 minute in a gamma counter.
13. Graph the standard curve using log-logit parameters with B0 tube as 100%. Read controls and unknown results off the standard curve.

Note: In Rat, the values obtained are divided by 2 to yield ng/ml Mouse values are read directly off the curve to yield ug/ml.

The assay is programmed for automated results on the Polymedco Iso Data Gamma Counter.

For Rats, with client agreemant, the assay may be run using less than 200 ul of specimen, and or in single.

QUALITY CONTROL

1. Final NSB cpm should be less than 3% of the total counts.
2. Maximum binding should be 25-35% of the total counts.
3. In each assay, include as control or recovery samples, previously assayed and/or TSH spiked samples. Recovered results should be targeted value plus or minus 20%.
4. If any of the above QC criteria are not acceptable, inform the director for determination of further action.

REAGENT SOURCES

PBS-Sigma
BSA-Sigma
NRS-Antibodies Incorporated or equivalent
RAT TSH purified for iodination -¦ Pituitary Hormones and
RAT TSH antibody ¦ Antisera Reference
RAT/MOUSE TSH reference prep. -¦ Center, UCLA, Ca.
Goat anti Rabbit precipitating reagent-DPC Incorporated

Note: Iodinated RAT TSH is obtained from Hazelton Laboratories America, Vienna, Va.

REFERENCES

Parlow, Albert F., Technical Report, Rat TSH package insert, Pituitary Hormones and Antisera Center.

Ottenweller, J.E., Hedge, G. A., (1982), Diurnal Variations of Plasma Thyrotropin, Thyroxine, and Triiodothyronine in Female Rats Are Phase Shifted After Inversion of the Photo-Period. Endocrinology 111: 509-514.

Loeb, W.F., Quimby, F.W., (eds) The Clinical Chemistry of Laboratory Animals, Pergamon Press, 1989.

PLEASE READ CAREFULLY

RAT THYROID STIMULATING HORMONE (rTSH RIA)

SOURCE OF rTSH IMMUNO-REAGENTS.

The rTSH RIA immuno-reagents were elaborated by

DR. A. F. PARLOW, DIRECTOR
PITUITARY HORMONES AND ANTISERA CENTER
HARBOR-UCLA MEDICAL CENTER
1000 WEST CARSON STREET
TORRANCE, CALIFORNIA 90509
TEL. #(213) 533-3537

DRAFT

ADDRESS TECHNICAL INQUIRIES TO DR. PARLOW

THE FOLLOWING IMMUNO-REAGENTS ARE PROVIDED:

1. RAT THYROID STIMULATING HORMONE ANTIGEN, highly purified, for iodination, rTSH-I-8 (AFP-8334B)
   1 vial, approx. 0.1 mg/vial, lyophilized, is provided. Store in desiccator in freezer.
2. RAT THYROID STIMULATING HORMONE ANTISERUM(rabbit), anti-rTSH-S-5(C21381)
   1.2 ml., in 2% normal rabbit serum (NRS) in phosphosaline buffer (PBS).
   Shipped in stable, liquid form. Store in freezer, on arrival.
3. RAT THYROID STIMULATING HORMONE REFERENCE PREPARATION, rTSH-RP-2 (AFP-5153B) for use as "cold" standard only, not for iodination.
   1 vial, 5 micrograms/vial, lyophilized in 1 ml of 1% BSA in phosphosaline buffer, is provided. Store in freezer. NOTE: rTSH-RP-2 IS 176 TIMES MORE POTENT THAN rTSH-RP-1.

A. RAT THYROID STIMULATING HORMONE ANTIGEN rTSH-I-8): STORAGE & IODINATION.
   To conserve this highly purified preparation, do NOT solubilize the entire contents of the vial of rTSH-I-8. Minutes prior to the first iodination, weigh off an aliquot of 20-50 micrograms, if possible. Solubilize this aliquot in PBS, at 100 micrograms/ml, using this solubilized material for iodination. Store the residual lyophilized rTSH-I-8 in a desiccator in a freezer, pending future use. Aliquots of the solubilized antigen can be prepared, and stored frozen FOR NOT LONGER THAN 2 TO 3 MONTHS, for subsequent iodinations. DO NOT RE-LYOPHILIZE THESE ALIQUOTS. For iodination by the Chloramine-T method, use NOT MORE THAN 4-6 micrograms Chloramine-T per microgram of rTSH-I-8 to be iodinated. High concentrations of Chloramine-T may "damage" the rTSH resulting in iodinated rTSH having sub-optimal immunoreactivity or poor stability. The goal is iodination to MODERATE specific activity. In striving for effective iodination, the concentration of Chloramine-T is the parameter to be experimentally varied. NOTE: rTSH for iodination, kept in solution (even frozen) for more than 2-3 months, may lose its ability to bind well with antiserum, after iodination. In case of such difficulty, you should solubilize another aliquot of the lyophilized powder, and use that for iodination. (Antisera deteriorate rarely. This is not the usual cause of problems
B. RAT THYROID STIMULATING HORMONE REFERENCE PREPARATION rTSH-RP-2): STORAGE
   For use as "cold standard", for displacement curves, rTSH-RP-2 should be reconstituted with 1 ml distilled water. This will provide a solution of 5 micrograms/ml in 1% BSA in phosphosaline. Aliquots of 25 microliters of this 5 micrograms/ml solution can then be prepared and stored frozen for a period of about 3-5 months.
   NOTE: rTSH-RP-2 is 176 times more potent than rTSH-RP-1. Therefore, the doses used to construct a "standard curve" should be 176 times lower. Also rat serum TSH values, expressed in terms of rTSH-RP-2 will be 176 times lower than values expressed in terms of rTSH-RP-1.

PLEASE TURN PAGE

C. PROCEDURE FOR RADIOIMMUNOASSAY OF RAT THYROID STIMULATING HORMONE

All reagents can be added to the RIA "tubes" at a single sitting, at refrigerator temperature, in the sequence a)buffer, b)"cold standard" or unknown, c)radio-iodinated rTSH-I- , & d)antiserum, at a final tube dilution of 1:10,000. The reagents can then be incubated at room temperature for 24 hours, prior to addition of "second" antibody.

Representative standard curves for rTSH-I- and rTSH-RP-2 are presented in a graph attached to this procedural guide. The graph also presents specificity information.

D. CHARACTERIZATION OF RAT THYROID STIMULATING HORMONE ANTIGEN rTSH-I-8

The biological potency of this preparation is 35 International Units per mg, as determined in the McKenzie Mouse Assay. Contamination of this preparation with rFSH is 1.5%, with rLH is 5% and with rGH and rPRL is less than 0.1%, as determined by radioimmunoassays.

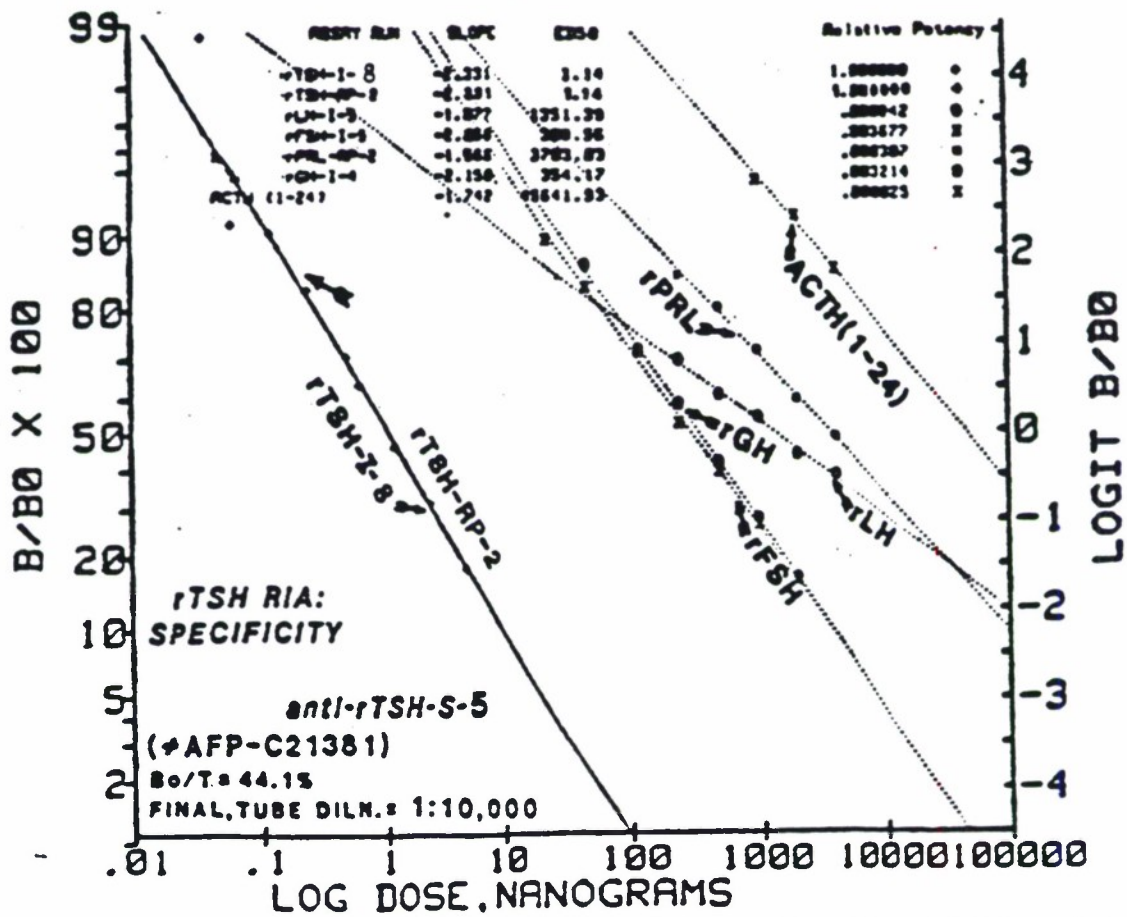
Chemical characterization of rTSH-I-8, by analytic Sephadex gel filtration, revealed it to be 95-100% monomeric.

E. CHARACTERIZATION OF RAT THYROID STIMULATING HORMONE ANTISERUM anti-rTSH-S-5

Specificity of this antiserum, in terms of its reactivity with anterior pituitary hormones other than thyroid stimulating hormone, was challenged with highly purified preparations of rGH, rFSH, rLH and rPRL. Data are displayed on an accompanying graph.

Sufficient antiserum has been provided to operate 15,000 RIA "tubes", if used at the recommended dilution.

anti-rTSH-S-5 was developed using as immunogen highly purified rat Thyroid Stimulating Hormone similar to rTSH-I-8.



TECHNICAL REPORT NUMBER 129 OF THE PITUITARY HORMONES AND ANTISERA CENTER.

3. CRUDE MOUSE TSH/LH REFERENCE PREPARATION, AFP51718MP for use as "cold standard" only, not for iodination. 1 ampoule, APPROX. 100 micrograms, lyophilized is provided. Store in freezer.

PLACED IN USE 2/94

APPENDIX 8

INDIVIDUAL HEMATOLOGY DATA

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Hematology Test Directory

STUDY: UIC-11B

NO.	ABBR. UNITS	DESCRIPTION PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT--- MALE	FEMALE	---UPPER LIMIT--- MALE	FEMALE
1.	RBC	Erythrocytes							
	10^6/mm^3	0.00	NO			9.00	8.00	12.00	11.00
2.	HGB	Hemoglobin							
	g/dL	0.0	NO			15.0	14.0	19.0	18.0
3.	HCT	Hematocrit							
	%	0.0	NO			45.0	43.0	55.0	53.0
4.	MCV	Mean Corpuscular Volume							
	fL	0.0	NO			45.0	45.0	55.0	55.0
5.	MCH	Mean Corpuscular Hemoglobin							
	pg	0.0	NO			15.0	15.0	20.0	20.0
6.	MCHC	Mean Corpus. Hemo. Conc.							
	g/dL	0.0	NO			30.0	30.0	37.0	37.0
7.	RETICS	Reticulocytes							
	% RBCs	0.0	NO			0.0	0.0	2.0	2.0
8.	PLT	Platelets							
	10^3/mm^3	Integer	NO			800	800	1300	1300
9.	WBC	Leukocytes							
	10^3/mm^3	0.0	NO			5.0	3.0	13.0	10.0

(END OF REPORT)

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 14

STUDY ID: UIC-11B
STUDY NO: 166
SEX: MALE

Animal ID	RBC 10^6/mm^3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	PLT 10^3/mm^3
GROUP: 1-M:0 mg/kg/day								
201	10.34	17.3	49.8	48.2	16.7	34.7	0.6	983
205	10.37	17.7	50.8	49.0	17.1	34.8	0.6	997
206	9.84	16.9	47.5	48.3	17.2	35.6	0.7	1119
207	10.78	18.1	52.4	48.6	16.8	34.5	0.6	857
210	10.57	18.1	52.2	49.4	17.1	34.7	0.5	856
MEAN	10.38	17.6	50.5	48.7	17.0	34.9	0.6	962
SD	0.350	0.52	2.00	0.50	0.22	0.43	0.07	110.2
N	5	5	5	5	5	5	5	5
GROUP: 2-M:1 mg/kg/day								
221	9.91	16.6	48.0	48.4	16.8	34.6	0.8	1215
225	9.57	16.3	46.8	48.9	17.0	34.8	0.5	1062
227	10.16	17.1	49.7	48.9	16.8	34.4	0.6	1037
228	9.46	16.4	46.1	48.7	17.3	35.6	0.5	1043
229	10.19	17.4	49.5	48.6	17.1	35.2	0.7	890
MEAN	9.86	16.8	48.0	48.7	17.0	34.9	0.6	1049
SD	0.334	0.47	1.60	0.21	0.21	0.48	0.13	115.3
N	5	5	5	5	5	5	5	5
GROUP: 3-M:5 mg/kg/day								
242	11.10	18.1	52.8	47.6	16.3	34.3	0.6	960
243	11.46	19.1	54.5	47.6	16.7	35.0	0.5	853
245	9.70	16.3	46.9	48.4	16.8	34.8	0.7	1179
248	10.33	17.6	49.7	48.1	17.0	35.4	0.9	1113
249	10.14	17.0	48.1	47.4	16.8	35.3	0.3	1103
MEAN	10.55	17.6	50.4	47.8	16.7	35.0	0.6	1042
SD	0.719	1.07	3.19	0.41	0.26	0.44	0.22	132.3
N	5	5	5	5	5	5	5	5

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 14

STUDY ID: UIC-11B
STUDY NO: 166
SEX: MALE

Animal ID	RBC 10^6/mm^3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	PLT 10^3/mm^3
GROUP: 4-M:25 mg/kg/day								
262	10.55	16.9	47.4	44.9	16.0	35.7	0.5	1075
264	10.39	16.6	47.1	45.3	16.0	35.2	0.3	1175
265	9.73	15.6	43.5	44.7	16.0	35.9	0.4	1295
267	10.04	16.3	46.0	45.8	16.2	35.4	0.7	1133
270	9.75	16.0	45.0	46.2	16.4	35.6	0.3	1175
MEAN	10.09	16.3	45.8	45.4	16.1	35.6	0.4	1171
SD	0.371	0.51	1.60	0.62	0.18	0.27	0.17	80.7
N	5	5	5	5	5	5	5	5

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 14

STUDY ID: UIC-11B
STUDY NO: 166
SEX: FEMALE

Animal ID	RBC 10^6/mm^3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	PLT 10^3/mm^3
GROUP: 1-F:0 mg/kg/day								
213	9.46	16.6	46.4	49.0	17.5	35.8	0.6	988
217	9.78	17.0	48.0	49.1	17.4	35.4	0.7	1145
218	9.98	17.5	49.7	49.8	17.5	35.2	0.5	851
219	9.63	16.5	47.1	48.9	17.1	35.0	0.6	929
220	10.03	17.6	49.6	49.5	17.5	35.5	0.8	652
MEAN	9.78	17.0	48.2	49.3	17.4	35.4	0.6	913
SD	0.238	0.50	1.47	0.38	0.17	0.30	0.11	181.4
N	5	5	5	5	5	5	5	5
GROUP: 2-F:1 mg/kg/day								
233	10.30	18.0	51.0	49.5	17.5	35.3	0.4	734
234	9.42	16.5	46.5	49.4	17.5	35.5	0.8	879
236	9.66	19.6	48.7	50.4	20.3	40.2	0.4	794
237	9.71	16.9	47.9	49.3	17.4	35.3	0.5	932
238	9.77	17.1	47.7	48.8	17.5	35.8	0.5	1034
MEAN	9.77	17.6	48.4	49.5	18.0	36.4	0.5	875
SD	0.324	1.24	1.67	0.58	1.26	2.12	0.16	117.2
N	5	5	5	5	5	5	5	5
GROUP: 3-F:5 mg/kg/day								
251	9.72	16.7	47.3	48.7	17.2	35.3	0.7	770
253	9.40	16.5	45.9	48.8	17.6	35.9	0.7	977
254	9.72	16.7	47.2	48.6	17.2	35.4	0.3	909
257	9.72	17.2	47.6	49.0	17.7	36.1	0.5	1108
260	9.76	16.9	47.6	48.8	17.3	35.5	0.3	1027
MEAN	9.66	16.8	47.1	48.8	17.4	35.6	0.5	958
SD	0.149	0.26	0.70	0.15	0.23	0.34	0.20	127.8
N	5	5	5	5	5	5	5	5

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 14

STUDY IO: UIC-11B
STUDY NO: 166
SEX: FEMALE

Animal ID	RBC 10^6/mm^3	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	PLT 10^3/mm^3
GROUP: 4-F:25 mg/kg/day								
272	9.48	16.0	44.9	47.4	16.9	35.6	0.4	1002
273	9.39	15.7	43.7	46.5	16.7	35.9	0.5	1099
274	9.32	16.0	43.5	46.7	17.2	36.8	0.3	920
277	9.73	16.7	46.3	47.6	17.2	36.1	0.2	983
279	9.28	15.6	43.3	46.7	16.8	36.0	0.7	1051
MEAN	9.44	16.0	44.3	47.0	17.0	36.1	0.4	1011
SD	0.179	0.43	1.26	0.49	0.23	0.44	0.19	68.0
N	5	5	5	5	5	5	5	5

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166 GROUP: 1-M : 0 mg/kg/day SEX: MALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
201	Nucleated Red Cells	0	
	M. Neutrophils	27.0	2.5
	I. Neutrophils	0.0	0.0
	Lymphocytes	71.0	6.5
	Monocytes	0.0	0.0
	Eosinophils	2.0	0.2
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		9.1
205	Nucleated Red Cells	0	
	M. Neutrophils	14.0	1.0
	I. Neutrophils	0.0	0.0
	Lymphocytes	82.0	6.1
	Monocytes	3.0	0.2
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		7.4
206	Nucleated Red Cells	0	
	M. Neutrophils	18.0	1.6
	I. Neutrophils	0.0	0.0
	Lymphocytes	74.0	6.5
	Monocytes	3.0	0.3
	Eosinophils	5.0	0.4
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		8.8
207	Nucleated Red Cells	0	
	M. Neutrophils	26.0	2.2
	I. Neutrophils	0.0	0.0
	Lymphocytes	74.0	6.1
	Monocytes	0.0	0.0
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		8.3

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166 GROUP: 1-M : 0 mg/kg/day SEX: MALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
210	Nucleated Red Cells	0	
	M. Neutrophils	16.0	0.6
	I. Neutrophils	0.0	0.0
	Lymphocytes	83.0	3.2
	Monocytes	0.0	0.0
	Eosinophils	1.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		3.9

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166

GROUP: 2-M : 1 mg/kg/day

SEX: MALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
221	Nucleated Red Cells	0	
	M. Neutrophils	15.0	1.2
	I. Neutrophils	0.0	0.0
	Lymphocytes	83.0	6.8
	Monocytes	2.0	0.2
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		8.2
225	Nucleated Red Cells	0	
	M. Neutrophils	25.0	1.2
	I. Neutrophils	0.0	0.0
	Lymphocytes	75.0	3.7
	Monocytes	0.0	0.0
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		4.9
227	Nucleated Red Cells	0	
	M. Neutrophils	10.0	0.7
	I. Neutrophils	0.0	0.0
	Lymphocytes	90.0	6.3
	Monocytes	0.0	0.0
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		7.0
228	Nucleated Red Cells	0	
	M. Neutrophils	11.0	0.7
	I. Neutrophils	0.0	0.0
	Lymphocytes	88.0	6.0
	Monocytes	0.0	0.0
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		6.8

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166

GROUP: 2-M : 1 mg/kg/day

SEX: MALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
229	Nucleated Red Cells	0	
	M. Neutrophils	10.0	0.5
	I. Neutrophils	0.0	0.0
	Lymphocytes	89.0	4.1
	Monocytes	1.0	0.0
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		4.6

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166 GROUP: 3-M : 5 mg/kg/day SEX: MALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
242	Nucleated Red Cells	0	
	M. Neutrophils	12.0	0.3
	I. Neutrophils	0.0	0.0
	Lymphocytes	88.0	2.5
	Monocytes	0.0	0.0
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		2.8
243	Nucleated Red Cells	0	
	M. Neutrophils	12.0	0.9
	I. Neutrophils	0.0	0.0
	Lymphocytes	87.0	6.6
	Monocytes	0.0	0.0
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		7.6
245	Nucleated Red Cells	0	
	M. Neutrophils	15.0	1.1
	I. Neutrophils	0.0	0.0
	Lymphocytes	85.0	6.0
	Monocytes	0.0	0.0
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		7.0
248	Nucleated Red Cells	0	
	M. Neutrophils	14.0	1.0
	I. Neutrophils	0.0	0.0
	Lymphocytes	86.0	6.2
	Monocytes	0.0	0.0
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		7.2

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166 GROUP: 3-M : 5 mg/kg/day SEX: MALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
249	Nucleated Red Cells	0	
	M. Neutrophils	20.0	1.8
	I. Neutrophils	0.0	0.0
	Lymphocytes	79.0	7.3
	Monocytes	1.0	0.1
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		9.2

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166 GROUP: 4-M : 25 mg/kg/day SEX: MALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
262	Nucleated Red Cells	0	
	M. Neutrophils	22.0	1.0
	I. Neutrophils	0.0	0.0
	Lymphocytes	77.0	3.5
	Monocytes	1.0	0.0
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		4.5
264	Nucleated Red Cells	0	
	M. Neutrophils	27.0	2.0
	I. Neutrophils	0.0	0.0
	Lymphocytes	70.0	5.2
	Monocytes	2.0	0.1
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		7.4
265	Nucleated Red Cells	0	
	M. Neutrophils	27.0	2.7
	I. Neutrophils	0.0	0.0
	Lymphocytes	70.0	7.0
	Monocytes	2.0	0.2
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		10.0
267	Nucleated Red Cells	0	
	M. Neutrophils	7.0	0.6
	I. Neutrophils	0.0	0.0
	Lymphocytes	93.0	8.1
	Monocytes	0.0	0.0
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		8.7

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-118
STUDY NO: 166 GROUP: 4-M : 25 mg/kg/day SEX: MALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
270	Nucleated Red Cells	0	
	M. Neutrophils	23.0	2.6
	I. Neutrophils	0.0	0.0
	Lymphocytes	73.0	8.2
	Monocytes	1.0	0.1
	Eosinophils	3.0	0.3
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		11.2

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166

GROUP: 1-F : 0 mg/kg/day

SEX: FEMALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
213	Nucleated Red Cells	0	
	M. Neutrophils	14.0	0.9
	I. Neutrophils	0.0	0.0
	Lymphocytes	84.0	5.6
	Monocytes	2.0	0.1
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		6.7
217	Nucleated Red Cells	0	
	M. Neutrophils	20.0	2.0
	I. Neutrophils	0.0	0.0
	Lymphocytes	78.0	7.8
	Monocytes	1.0	0.1
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		10.0
218	Nucleated Red Cells	0	
	M. Neutrophils	26.0	1.4
	I. Neutrophils	2.0	0.1
	Lymphocytes	68.0	3.6
	Monocytes	2.0	0.1
	Eosinophils	2.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		5.3
219	Nucleated Red Cells	0	
	M. Neutrophils	27.0	1.8
	I. Neutrophils	0.0	0.0
	Lymphocytes	71.0	4.8
	Monocytes	1.0	0.1
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		6.8

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-118
STUDY NO: 166

GROUP: 1-F : 0 mg/kg/day

SEX: FEMALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
220	Nucleated Red Cells	0	
	M. Neutrophils	11.0	0.5
	I. Neutrophils	0.0	0.0
	Lymphocytes	88.0	4.0
	Monocytes	0.0	0.0
	Eosinophils	1.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		4.5

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166

GROUP: 2-F : 1 mg/kg/day

SEX: FEMALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
233	Nucleated Red Cells	0	
	M. Neutrophils	12.0	0.7
	I. Neutrophils	0.0	0.0
	Lymphocytes	83.0	5.1
	Monocytes	1.0	0.1
	Eosinophils	4.0	0.2
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		6.1
234	Nucleated Red Cells	0	
	M. Neutrophils	4.0	0.2
	I. Neutrophils	0.0	0.0
	Lymphocytes	95.0	5.7
	Monocytes	1.0	0.1
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		6.0
236	Nucleated Red Cells	0	
	M. Neutrophils	11.0	0.6
	I. Neutrophils	0.0	0.0
	Lymphocytes	85.0	4.8
	Monocytes	3.0	0.2
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		5.6
237	Nucleated Red Cells	0	
	M. Neutrophils	12.0	0.8
	I. Neutrophils	0.0	0.0
	Lymphocytes	86.0	5.8
	Monocytes	1.0	0.1
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		6.8

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166

GROUP: 2-F : 1 mg/kg/day

SEX: FEMALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
238	Nucleated Red Cells	0	
	M. Neutrophils	15.0	1.1
	I. Neutrophils	0.0	0.0
	Lymphocytes	83.0	6.2
	Monocytes	1.0	0.1
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		7.5

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166

GROUP: 3-F : 5 mg/kg/day

SEX: FEMALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
251	Nucleated Red Cells	0	
	M. Neutrophils	16.0	0.8
	I. Neutrophils	0.0	0.0
	Lymphocytes	81.0	4.2
	Monocytes	2.0	0.1
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		5.2
253	Nucleated Red Cells	0	
	M. Neutrophils	18.0	1.3
	I. Neutrophils	1.0	0.1
	Lymphocytes	73.0	5.1
	Monocytes	5.0	0.4
	Eosinophils	3.0	0.2
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		7.0
254	Nucleated Red Cells	0	
	M. Neutrophils	6.0	0.3
	I. Neutrophils	0.0	0.0
	Lymphocytes	93.0	5.0
	Monocytes	0.0	0.0
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		5.4
257	Nucleated Red Cells	0	
	M. Neutrophils	21.0	1.1
	I. Neutrophils	0.0	0.0
	Lymphocytes	70.0	3.8
	Monocytes	4.0	0.2
	Eosinophils	5.0	0.3
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		5.4

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166

GROUP: 3-F : 5 mg/kg/day

SEX: FEMALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
260	Nucleated Red Cells	0	
	M. Neutrophils	17.0	0.6
	I. Neutrophils	0.0	0.0
	Lymphocytes	82.0	3.1
	Monocytes	0.0	0.0
	Eosinophils	1.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		3.8

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166 GROUP: 4-F : 25 mg/kg/day SEX: FEMALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
272	Nucleated Red Cells	0	
	M. Neutrophils	22.0	2.1
	I. Neutrophils	0.0	0.0
	Lymphocytes	78.0	7.5
	Monocytes	0.0	0.0
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		9.6
273	Nucleated Red Cells	0	
	M. Neutrophils	29.0	2.0
	I. Neutrophils	0.0	0.0
	Lymphocytes	69.0	4.8
	Monocytes	2.0	0.1
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		7.0
274	Nucleated Red Cells	0	
	M. Neutrophils	7.0	0.6
	I. Neutrophils	0.0	0.0
	Lymphocytes	91.0	7.6
	Monocytes	2.0	0.2
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		8.3
277	Nucleated Red Cells	0	
	M. Neutrophils	11.0	0.9
	I. Neutrophils	0.0	0.0
	Lymphocytes	87.0	7.2
	Monocytes	2.0	0.2
	Eosinophils	0.0	0.0
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		8.3

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-11B
STUDY NO: 166 GROUP: 4-F : 25 mg/kg/day SEX: FEMALE

Animal ID		WEEK 14 REL	WEEK 14 ABS
279	Nucleated Red Cells	0	
	M. Neutrophils	15.0	0.8
	I. Neutrophils	0.0	0.0
	Lymphocytes	83.0	4.3
	Monocytes	1.0	0.1
	Eosinophils	1.0	0.1
	Basophils	0.0	0.0
	Atypical Lymphocytes	0.0	0.0
	WBC		5.2

APPENDIX 9

OPHTHALMOLOGY REPORT

ANIMAL EYE ASSOCIATES

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DRAFT

May 23, 1995

OPHTHALMIC REPORT

UIC/TRL Study No. 166

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

During Week -1 (February 14, 1995), a sufficient number of mice were given ophthalmic examinations by indirect ophthalmoscopy to result in forty males and forty females which were within normal limits.

During Week 13 (May 16, 1995), eighty mice which were used in the above-referenced study were re-examined. All mice appeared similar (no lesions) to their pretest examinations performed on February 14, 1995.

Sincerely,

Samuel J. Vainisi, D.V.M.
Professor of Comparative
Ophthalmology, U. of IL. at Chicago

Diplomate, American College of
Veterinary Ophthalmologists

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

Ophthalmic Examinations

Males

Dose	Animal Number	Week -1 R.E.	Week -1 L.E.	Week 13 R.E.	Week 13 L.E.
0	201	WNL	WNL	WNL	WNL
	202	WNL	WNL	WNL	WNL
	203	WNL	WNL	WNL	WNL
	204	WNL	WNL	WNL	WNL
	205	WNL	WNL	WNL	WNL
	206	WNL	WNL	WNL	WNL
	207	WNL	WNL	WNL	WNL
	208	WNL	WNL	WNL	WNL
	209	WNL	WNL	WNL	WNL
	210	WNL	WNL	WNL	WNL
1	221	WNL	WNL	WNL	WNL
	222	WNL	WNL	WNL	WNL
	223	WNL	WNL	WNL	WNL
	224	WNL	WNL	WNL	WNL
	225	WNL	WNL	WNL	WNL
	226	WNL	WNL	WNL	WNL
	227	WNL	WNL	WNL	WNL
	228	WNL	WNL	WNL	WNL
	229	WNL	WNL	WNL	WNL
	230	WNL	WNL	WNL	WNL

Dose = mg/kg/day
R.E. = Right Eye
L.E. = Left Eye
WNL = Within Normal Limits

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

Ophthalmic Examinations

Males (contd.)

Dose	Animal Number	Week -1 R.E.	Week -1 L.E.	Week 13 R.E.	Week 13 L.E.
5	241	WNL	WNL	WNL	WNL
	242	WNL	WNL	WNL	WNL
	243	WNL	WNL	WNL	WNL
	244	WNL	WNL	WNL	WNL
	245	WNL	WNL	WNL	WNL
	246	WNL	WNL	WNL	WNL
	247	WNL	WNL	WNL	WNL
	248	WNL	WNL	WNL	WNL
	249	WNL	WNL	WNL	WNL
	250	WNL	WNL	WNL	WNL
25	261	WNL	WNL	WNL	WNL
	262	WNL	WNL	WNL	WNL
	263	WNL	WNL	WNL	WNL
	264	WNL	WNL	WNL	WNL
	265	WNL	WNL	WNL	WNL
	266	WNL	WNL	WNL	WNL
	267	WNL	WNL	WNL	WNL
	268	WNL	WNL	WNL	WNL
	269	WNL	WNL	WNL	WNL
	270	WNL	WNL	WNL	WNL

Dose = mg/kg/day
R.E. = Right Eye
L.E. = Left Eye
WNL= Within Normal Limits

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

Ophthalmic Examinations

Females

Dose	Animal Number	Week -1 R.E.	Week -1 L.E.	Week 13 R.E.	Week 13 L.E.
0	211	WNL	WNL	WNL	WNL
	212	WNL	WNL	WNL	WNL
	213	WNL	WNL	WNL	WNL
	214	WNL	WNL	WNL	WNL
	215	WNL	WNL	WNL	WNL
	216	WNL	WNL	WNL	WNL
	217	WNL	WNL	WNL	WNL
	218	WNL	WNL	WNL	WNL
	219	WNL	WNL	WNL	WNL
	220	WNL	WNL	WNL	WNL
1	231	WNL	WNL	WNL	WNL
	232	WNL	WNL	WNL	WNL
	233	WNL	WNL	WNL	WNL
	234	WNL	WNL	WNL	WNL
	235	WNL	WNL	WNL	WNL
	236	WNL	WNL	WNL	WNL
	237	WNL	WNL	WNL	WNL
	238	WNL	WNL	WNL	WNL
	239	WNL	WNL	WNL	WNL
	240	WNL	WNL	WNL	WNL

Dose = mg/kg/day
R.E. = Right Eye
L.E. = Left Eye
WNL= Within Normal Limits

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

Ophthalmic Examinations

Females (contd.)

Dose	Animal Number	Week -1		Week 13	
		R.E.	L.E.	R.E.	L.E.
5	251	WNL	WNL	WNL	WNL
	252	WNL	WNL	WNL	WNL
	253	WNL	WNL	WNL	WNL
	254	WNL	WNL	WNL	WNL
	255	WNL	WNL	WNL	WNL
	256	WNL	WNL	WNL	WNL
	257	WNL	WNL	WNL	WNL
	258	WNL	WNL	WNL	WNL
	259	WNL	WNL	WNL	WNL
	260	WNL	WNL	WNL	WNL
25	271	WNL	WNL	WNL	WNL
	272	WNL	WNL	WNL	WNL
	273	WNL	WNL	WNL	WNL
	274	WNL	WNL	WNL	WNL
	275	WNL	WNL	WNL	WNL
	276	WNL	WNL	WNL	WNL
	277	WNL	WNL	WNL	WNL
	278	WNL	WNL	WNL	WNL
	279	WNL	WNL	WNL	WNL
	280	WNL	WNL	WNL	WNL

Dose = mg/kg/day
R.E. = Right Eye
L.E. = Left Eye
WNL= Within Normal Limits

APPENDIX 10

INDIVIDUAL ORGAN WEIGHT DATA

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: MALE
GROUP: 1-M - 0 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	201	202	203	204	205	206	207	208	209
BODY WEIGHT (G)	27.2	28.6	31.3	29.8	31.9	28.7	29.5	31.2	28.4
Brain (G)	0.463	0.471	0.471	0.499	0.506	0.495	0.453	0.468	0.448
Heart (G)	0.168	0.159	0.176	0.173	0.175	0.169	0.142	0.174	0.142
Kidneys (G)	0.500	0.507	0.600	0.577	0.572	0.550	0.484	0.505	0.481
Liver (G)	1.445	1.353	1.817	1.529	1.527	1.528	1.569	1.635	1.241
Lungs/Bronchi (G)	0.294	0.237	0.317	0.278	0.356	0.264	0.309	0.354	0.213
Spleen (G)	0.060	0.056	0.076	0.059	0.078	0.064	0.066	0.104	0.068
Testes (G)	0.240	0.250	0.243	0.242	0.279	0.270	0.225	0.271	0.239

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: MALE
GROUP: 1-M - 0 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID:	210
BALANCE NO.:	
BODY WEIGHT (G)	32.2
Brain (G)	0.486
Heart (G)	0.209
Kidneys (G)	0.600
Liver (G)	1.861
Lungs/Bronchi (G)	0.367
Spleen (G)	0.076
Testes (G)	0.210

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: MALE
GROUP: 2-M - 1 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	221	222	223	224	225	226	227	228	229
BODY WEIGHT (G)	30.8	29.4	33.0	30.5	30.1	31.7	30.7	30.2	30.5
Brain (G)	0.448	0.485	0.475	0.505	0.468	0.482	0.456	0.498	0.429
Heart (G)	0.172	0.145	0.172	0.165	0.173	0.158	0.173	0.217	0.209
Kidneys (G)	0.435	0.524	0.543	0.561	0.505	0.554	0.537	0.639	0.538
Liver (G)	1.585	1.505	1.795	1.413	1.623	1.625	1.670	1.799	1.662
Lungs/Bronchi (G)	0.167	0.313	0.340	0.331	0.265	0.301	0.285	0.348	0.300
Spleen (G)	0.063	0.066	0.073	0.088	0.075	0.062	0.050	0.073	0.081
Testes (G)	0.130	0.253	0.255	0.270	0.203	0.265	0.223	0.253	0.168

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: MALE
GROUP: 2-M - 1 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID:	230
BALANCE NO.:	
BODY WEIGHT (G)	30.5
Brain (G)	0.452
Heart (G)	0.211
Kidneys (G)	0.594
Liver (G)	1.619
Lungs/Bronchi (G)	0.235
Spleen (G)	0.058
Testes (G)	0.239

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: MALE
GROUP: 3-M - 5 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	241	242	243	244	245	246	247	248	249
BODY WEIGHT (G)	27.7	30.3	30.7	30.6	30.1	31.3	31.0	29.6	30.4
Brain (G)	0.465	0.621	0.480	0.473	0.477	0.466	0.470	0.467	0.485
Heart (G)	0.150	0.160	0.186	0.159	0.166	0.160	0.160	0.191	0.176
Kidneys (G)	0.481	0.545	0.495	0.566	0.545	0.551	0.524	0.565	0.545
Liver (G)	1.303	1.720	1.530	1.629	1.677	1.575	1.651	1.614	1.703
Lungs/Bronchi (G)	0.276	0.323	0.285	0.339	0.275	0.281	0.286	0.329	0.306
Spleen (G)	0.071	0.095	0.057	0.073	0.056	0.056	0.083	0.071	0.076
Testes (G)	0.245	0.229	0.240	0.254	0.252	0.197	0.254	0.255	0.247

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: MALE
GROUP: 3-M - 5 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID:	250
BALANCE NO.:	
BODY WEIGHT (G)	34.4
Brain (G)	0.486
Heart (G)	0.172
Kidneys (G)	0.651
Liver (G)	1.652
Lungs/Bronchi (G)	0.266
Spleen (G)	0.051
Testes (G)	0.246

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: MALE
GROUP: 4-M - 25 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	261	262	263	264	265	266	267	268	269
BODY WEIGHT (G)	30.5	28.0	30.3	31.9	29.2	27.6	30.0	29.3	29.7
Brain (G)	0.484	0.452	0.472	0.476	0.481	0.485	0.455	0.452	0.502
Heart (G)	0.166	0.184	0.159	0.181	0.195	0.149	0.156	0.153	0.156
Kidneys (G)	0.534	0.515	0.526	0.539	0.543	0.488	0.477	0.490	0.562
Liver (G)	1.589	1.557	1.595	1.696	1.656	1.439	1.675	1.303	1.503
Lungs/Bronchi (G)	0.322	0.297	0.350	0.346	0.235	0.267	0.263	0.236	0.341
Spleen (G)	0.060	0.060	0.054	0.059	0.068	0.074	0.060	0.082	0.083
Testes (G)	0.240	0.218	0.236	0.249	0.240	0.244	0.235	0.229	0.278

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: MALE
GROUP: 4-M - 25 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID:	270
BALANCE NO.:	
BODY WEIGHT (G)	31.9
Brain (G)	0.506
Heart (G)	0.187
Kidneys (G)	0.563
Liver (G)	1.822
Lungs/Bronchi (G)	0.306
Spleen (G)	0.073
Testes (G)	0.280

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STU[redacted]: 166
SEX[redacted] FEMALE
GROUP: 1-F - 0 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

[redacted] ID: / [redacted] NO.:	211	212	213	214	215	216	217	218	219
ODY WEIGHT (G)	27.5	29.5	30.4	24.8	26.1	26.0	26.0	28.0	26.1
rai[redacted]G)	0.482	0.454	0.506	0.463	0.474	0.466	0.495	0.490	0.427
eart (G)	0.143	0.159	0.157	0.121	0.135	0.125	0.142	0.140	0.143
id[redacted]s (G)	0.396	0.373	0.392	0.344	0.382	0.325	0.341	0.374	0.342
iver (G)	1.408	1.524	1.527	1.256	1.278	1.278	1.417	1.362	1.303
ung Bronchi (G)	0.313	0.328	0.271	0.194	0.265	0.213	0.301	0.301	0.216
pleen (G)	0.086	0.102	0.086	0.103	0.110	0.071	0.099	0.092	0.085

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: FEMALE
GROUP: 1-F - 0 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID:	220
BALANCE NO.:	
BODY WEIGHT (G)	27.2
Brain (G)	0.489
Heart (G)	0.137
Kidneys (G)	0.342
Liver (G)	1.387
Lungs/Bronchi (G)	0.289
Spleen (G)	0.073

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: FEMALE
GROUP: 2-F - 1 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	231	232	233	234	235	236	237	238	239
BODY WEIGHT (G)	28.5	24.9	27.5	28.5	31.3	26.9	26.1	29.3	31.2
Brain (G)	0.468	0.459	0.512	0.472	0.486	0.488	0.475	0.495	0.504
Heart (G)	0.160	0.134	0.113	0.130	0.158	0.160	0.149	0.131	0.153
Kidneys (G)	0.376	0.338	0.384	0.368	0.392	0.371	0.348	0.382	0.405
Liver (G)	1.465	1.285	1.423	1.519	1.591	1.338	1.381	1.380	1.636
Lungs/Bronchi (G)	0.208	0.175	0.298	0.267	0.290	0.337	0.287	0.233	0.240
Spleen (G)	0.094	0.090	0.095	0.089	0.105	0.083	0.092	0.076	0.107

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: FEMALE
GROUP: 2-F - 1 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID:	240
BALANCE NO.:	
BODY WEIGHT (G)	28.6
Brain (G)	0.501
Heart (G)	0.152
Kidneys (G)	0.371
Liver (G)	1.555
Lungs/Bronchi (G)	0.253
Spleen (G)	0.100

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: FEMALE
GROUP: 3-F - 5 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	251	252	253	254	255	256	257	258	259
BODY WEIGHT (G)	26.7	26.2	26.6	29.3	26.9	29.1	28.8	28.7	30.3
Brain (G)	0.470	0.491	0.466	0.484	0.480	0.483	0.494	0.517	0.503
Heart (G)	0.157	0.148	0.147	0.155	0.152	0.161	0.161	0.151	0.110
Kidneys (G)	0.354	0.369	0.335	0.416	0.369	0.404	0.362	0.418	0.387
Liver (G)	1.392	1.338	1.405	1.580	1.495	1.515	1.522	1.620	1.525
Lungs/Bronchi (G)	0.323	0.256	0.236	0.287	0.294	0.201	0.289	0.238	0.297
Spleen (G)	0.087	0.102	0.091	0.110	0.094	0.099	0.090	0.125	0.085

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: FEMALE GROUP: 3-F - 5 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID:	260
BALANCE NO.:	
BODY WEIGHT (G)	27.6
Brain (G)	0.465
Heart (G)	0.135
Kidneys (G)	0.382
Liver (G)	1.350
Lungs/Bronchi (G)	0.245
Spleen (G)	0.075

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: FEMALE
GROUP: 4-F - 25 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID: / BALANCE NO.:	271	272	273	274	275	276	277	278	279
BODY WEIGHT (G)	27.0	26.7	27.2	26.7	24.7	28.0	27.1	28.9	27.4
Brain (G)	0.481	0.499	0.474	0.492	0.460	0.492	0.498	0.516	0.492
Heart (G)	0.163	0.147	0.131	0.166	0.146	0.130	0.157	0.163	0.156
Kidneys (G)	0.343	0.369	0.374	0.350	0.335	0.358	0.359	0.435	0.375
Liver (G)	1.536	1.413	1.485	1.535	1.343	1.505	1.425	1.475	1.504
Lungs/Bronchi (G)	0.314	0.201	0.217	0.200	0.258	0.209	0.289	0.308	0.252
Spleen (G)	0.113	0.076	0.096	0.095	0.099	0.097	0.091	0.088	0.063

DRAFT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE

INDIVIDUAL ORGAN WEIGHTS

STUDY: 166
SEX: FEMALE
GROUP: 4-F - 25 mg/kg/day
FATES: SCHEDULED SACRIFICE DAYS: 91-92 ALL BALANCES

ANIMAL ID:	280
BALANCE NO.:	
BODY WEIGHT (G)	25.1
Brain (G)	0.491
Heart (G)	0.125
Kidneys (G)	0.292
Liver (G)	1.281
Lungs/Bronchi (G)	0.241
Spleen (G)	0.083

DRAFT

APPENDIX 11

PATHOLOGY REPORT

DRAFT PATHOLOGY REPORT FOR THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE UIC/TRL STUDY NUMBER 166

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OCTOBER 12, 1995

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SECTION I

PATHOLOGY NARRATIVE

DRAFT PATHOLOGY REPORT

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

INTRODUCTION

This pathology report, submitted by Pathology Associates International (PAI) to Toxicology Research Laboratory (TRL), University of Illinois at Chicago, represents the histopathology findings for the study designated as "Three Month Oral (Gavage) Toxicity Study of Halofantrine Hydrochloride in Mice", UIC/TRL Study Number 166.

EXPERIMENTAL DESIGN AND METHODS

Four groups, each composed of 10 male and 10 female B6C3F1 (Virus Antibody Free) mice, received control or test article formulations by oral gavage. Dose groups, dose levels, and animals per group are detailed in the Summary of Experimental Design (Table I). All animals received vehicle or test substance once daily for at least 13 weeks.

All animals survived until the scheduled terminal sacrifice and were sacrificed and necropsied by PAI personnel. Necropsies were performed according to TRL Standard Operating Procedures. Tissues required by the protocol for collection and fixation at necropsy were examined and fixed in 10% neutral buffered formalin (see Table II, Protocol-Required Tissues for Necropsy and Histopathology). Tissues required for histopathologic evaluation were trimmed, processed, and slides were prepared in accordance with PAI Standard Operating Procedures. Slides were prepared for all protocol-required tissues for high dose and control animals and were evaluated by light microscopy. Based on initial histopathology evaluations, liver and kidney for all low and mid dose animals, and thymus for low and mid dose males were examined histologically. Tissues were only designated as unavailable after examination of blocks and/or wet tissues and failure to find the tissue in recuts and/or retrims.

Microscopic findings for all groups are summarized in the Project Summary Tables (Section II). The mean group severity scores are found in the Severity Summary Tables (Section III). The mean group severity scores were determined by dividing the sum of all severity scores for a finding by the number of tissues examined. Microscopic findings in the protocol-required tissues for individual animals are presented in the Tabulated Animal Data Tables (Section IV). The correlation of the necropsy findings and histopathology findings are reported in the Correlation of Gross and Microscopic (Micro) Findings (Section V). The codes used as entries in these tables are explained in the Report Codes Table.

RESULTS AND DISCUSSION

The Results and Discussion section is divided into three parts: Necropsy Findings, Diagnostic Terms, and Histopathology Findings. The Necropsy Findings portion identifies lesions seen at necropsy that were test article-related. The Diagnostic Terms

portion lists and clarifies diagnostic terminology that may be unclear. Terms listed in the Diagnostic Terms portion of this section were not necessarily considered to be test article-related. The Histopathology Findings portion of this section reports the results and provides discussion of the histopathologic evaluation of the tissues.

Necropsy Findings

Gross lesions were not observed at necropsy in either males or females in this study.

Diagnostic Terms

The morphologic characteristics of observations and lesions which require comment are presented in subsequent paragraphs to aid in the interpretation of the data.

Liver

Glycogen depletion was characterized by hepatocytes that lacked coarsely vacuolated cytoplasm characteristic of hepatocytes from unfasted animals. Affected hepatocytes had more deeply and uniformly eosinophilic cytoplasm. Only centrilobular regions were involved for minimally affected animals, but the entire lobule was affected for moderately affected animals. Individual cell necrosis was characterized by the presence of small foci of cellular debris in hepatic parenchyma, primarily in periportal regions.

Thymus

Hemorrhage was characterized by the presence of one or more foci wherein erythrocytes were present in the thymic parenchyma.

Stomach

Subacute inflammation was characterized by infiltration of lymphocytes and neutrophils in the submucosal stroma of the glandular mucosa.

Kidney

Nephropathy was indicated by the presence of basophilic tubules that were interpreted as tubular regeneration. All incidences observed in this study consisted of a single focal area in one kidney from the affected animal. Chronic inflammation in the cortex was characterized by an interstitial infiltrate of lymphocytes.

Brain

The meningioma in brain from animal number 279 (high dose female) consisted of a small nodule on the meningeal surface between cerebellar folia. Cells within the nodule varied from round to spindle in shape and contained a moderate to copious amount of homogeneous eosinophilic cytoplasm. Cell nuclei were also round to spindle in shape, were fairly large, and contained finely granular chromatin with a very small nucleolus.

The remainder of the diagnoses used in this study were considered to be self-explanatory and are not discussed in this section.

Histopathology Findings

Histopathology findings that are considered to be treatment-related are summarized in Table III and presented in this section. Histopathology findings that require discussion to assess relationship to treatment are also discussed in this section.

Liver

Glycogen depletion was observed in liver from 8 of 10 (sev=1.0), 8 of 10 (sev=0.9), 10 of 10 (sev=1.1), and 10 of 10 (sev=1.9) male mice in Groups 1, 2, 3, and 4, respectively. Glycogen depletion was observed in liver from 2 of 10 (sev=0.2), 2 of 10 (sev=0.2), 1 of 10 (sev=0.1), and 8 of 10 (sev=1.3) female mice in Groups 1, 2, 3, and 4, respectively. Glycogen depletion was interpreted as a treatment-related change because of the increase in incidence and/or mean group severity in both male and female mice in Group 4 when compared to Groups 1, 2, and 3. The glycogen depletion observed in these non-fasted animals is typical of that seen in animals which are fasted. Glycogen depletion could therefore result from either reduced diet consumption or a direct metabolic effect of treatment on the liver.

Individual cell necrosis was observed in liver from 0 of 10 (sev=0.0), 0 of 10 (sev=0.0), 0 of 10 (sev=0.0), and 2 of 10 (sev=0.2) female mice in Groups 1, 2, 3, and 4, respectively. Individual cell necrosis was interpreted as a treatment-related change because of the increased incidence observed in female mice in Group 4 when compared to Groups 1, 2, and 3.

Thymus

Hemorrhage was observed in thymus from 0 of 10 (sev=0.0), 1 of 10 (sev=0.1), 0 of 10 (sev=0.0), and 2 of 10 (sev=0.2) male mice in groups 1, 2, 3, and 4, respectively. Also, hemorrhage was observed in thymus from 1 of 10 (sev=0.1) and 0 of 10 (sev=0.0) female mice in Groups 1 and 4, respectively. Thymus was not examined in females in Groups 2 and 3. Hemorrhage in thymus was not interpreted as a treatment-related change because it occurs occasionally in control animals, including one female control in this study, and a clear dose-dependence was not apparent in males after evaluation of thymus in all treatment groups.

Kidney

Chronic inflammation was observed in cortex of kidney from 1 of 10 (sev=0.1), 1 of 10 (sev=0.1), 1 of 10 (sev=0.1), and 4 of 10 (sev=0.4) male mice in Groups 1, 2, 3, and 4, respectively. Chronic inflammation was observed in cortex of kidney in 1 of 10 (sev=0.1), 3 of 10 (sev=0.3), 3 of 10 (sev=0.3), and 1 of 10 (sev=0.1) female mice in Groups 1, 2, 3, and 4, respectively. Chronic inflammation in cortex of kidney was not interpreted as a treatment-related change because it often occurs as an incidental finding and a dose-dependent relationship is lacking in female mice.

Nephropathy was observed in kidney from 0 of 10 (sev=0.0), 0 of 10 (sev=0.0), 0 of 10 (sev=0.0), and 1 of 10 (sev=0.1) male mice in Groups 1, 2, 3, and 4, respectively. Nephropathy was observed in kidney from 0 of 10 (sev=0.0), 0 of 10 (sev=0.0), 0 of 10 (sev=0.0), and 1 of 10 (sev=0.1) female mice in Groups 1, 2, 3, and 4, respectively. Nephropathy was not interpreted as a treatment-related finding because it occasionally occurs in control animals (not in this study) and the incidence and severity were very low in both sexes.

Stomach

Subacute inflammation was observed in glandular mucosa of stomach in 0 of 10 (sev=0.0) and 1 of 10 (sev=0.2) female mice in Groups 1 and 4, respectively. Subacute inflammation in stomach was not interpreted as a treatment-related finding because of the low incidence and because it is occasionally present in control animals (not in this study).

Other Lesions

The small meningioma in brain from animal number 279 (Group 4, 25 mg/kg/day) is an uncommon finding in a 13 week study, but it is considered incidental in the absence of carcinogenicity study results. All other lesions are considered to be incidental changes that are not related to test article treatment.

CONCLUSIONS

Under the conditions of this study, administration of 25 mg/kg/day of halofantrine hydrochloride by oral gavage for thirteen weeks resulted in glycogen depletion and individual cell necrosis in liver. The incidence and severity of glycogen depletion and individual cell necrosis in liver from mice treated with 5 or 1 mg/kg/day were not significantly different from the incidence and severity in control animals. Based on histopathology findings, the no-effect treatment level for this study was 5 mg/kg/day.

_____ _____

Robert L Morrissey, DVM, Ph.D. Date
Diplomate, ACVP

TABLE I

SUMMARY OF EXPERIMENTAL DESIGN

Treatment Group	Dose Level (mg/kg/day)	Number of Males	Number of Females
1	0	10	10
2	1	10	10
3	5	10	10
4	25	10	10

TABLE II

PROTOCOL-REQUIRED TISSUES FOR NECROPSY AND HISTOPATHOLOGY

Adrenal glands
Brain
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes with harderian glands
Femur with marrow
Gallbladder
Heart
Ileum
Jejunum
Kidneys
Liver
Lungs with bronchi
Lymph node (mesenteric)
Mammary gland
Ovaries
Pancreas
Parathyroid gland
Pituitary gland
Prostate
Salivary gland (submaxillary)
Sciatic nerve
Skeletal muscle
Skin (abdominal)
Spinal cord (thoracic)
Spleen
Stomach
Testes
Thymus
Thyroid gland
Tongue
Trachea
Ureter
Urinary bladder
Uterus
Vagina

Gross lesions

TABLE III

SUMMARY OF TREATMENT-RELATED LESIONS

MICROSCOPIC LESIONS		GROUP NUMBER[a]			
ORGAN-Lesion	Sex	1	2	3	4
LIVER					
-Depletion, glycogen	M	8/10 (1.00)b	8/10 (0.90)	10/10 (1.10)	10/10 (1.90)
	F	2/10 (0.20)	2/10 (0.20)	1/10 (0.10)	8/10 (1.30)
-Necrosis, individual cell	M	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)
	F	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	2/10 (0.20)

[a] Group 1: 0 mg/kg/day
Group 2: 1 mg/kg/day
Group 3: 5 mg/kg/day
Group 4: 25 mg/kg/day

[b] Incidence (mean group severity) = Mean group severity scores were determined by dividing the sum of all severity scores for a finding by the number of tissues examined.

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY
STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

Report Codes Table

A. Codes applying to organs

N	Tissues within normal histological limits
A	Autolysis precluding adequate evaluation
O	Paired organ missing
U	Tissues unavailable/unsuitable for complete evaluation
S	Tissues not applicable to animal
*	Tissues not required by protocol

B. Codes applying to microscopic diagnoses

1	minimal
2	mild
3	moderate
4	marked
( )	focal
[ ]	diffuse
< >	multifocal
P	Present
B	Neoplasm, benign
M	Neoplasm, malignant without metastasis
C	Neoplasm, malignant with metastasis
X	Metastatic site (+)
I	Bilateral
L	Unilateral
-	No data entered

SECTION II

PROJECT SUMMARY TABLE

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

PROJECT SUMMARY

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL
SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1		2		3		4	
		(1)		(2)		(3)		(4)	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
BRAIN	# EX	10		0		0		10	
PITUITARY GLAND	# EX	9		0		0		8	
THYMUS	# EX	10		10		10		10	
Hemorrhage, focal		0	0.0	1	10.0	0	0.0	2	20.0
SALIVARY GLAND	# EX	10		0		0		10	
SPINAL CORD (THORACIC)	# EX	10		0		0		10	
ADRENAL GLAND	# EX	10		0		0		10	
Ectopic adrenal		0	0.0	0	0.0	0	0.0	1	10.0
THYROID GLAND	# EX	10		0		0		10	
PARATHYROID GLAND	# EX	9		0		0		9	
Cyst		1	11.0	0	0.0	0	0.0	0	0.0
TRACHEA	# EX	10		0		0		10	
ESOPHAGUS	# EX	10		0		0		10	
HEART	# EX	10		0		0		10	
DUODENUM	# EX	10		0		0		10	
COLON	# EX	10		0		0		10	
STOMACH	# EX	10		0		0		10	
Cyst, glandular mucosa		1	10.0	0	0.0	0	0.0	0	0.0

Incidence Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

PROJECT SUMMARY

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL

SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1 (1)		2 (2)		3 (3)		4 (4)	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
LIVER	# EX	10		10		10		10	
Depletion, glycogen		8	80.0	8	80.0	10	100.0	10	100.0
GALLBLADDER	# EX	10		0		0		9	
SPLEEN	# EX	10		0		0		10	
JEJUNUM	# EX	10		0		0		10	
LUNG	# EX	10		0		0		10	
Inflammation, chronic, peribronchial		0	0.0	0	0.0	0	0.0	1	10.0
KIDNEY	# EX	10		10		10		10	
Inflammation, chronic, cortex		1	10.0	1	10.0	1	10.0	4	40.0
Nephropathy		0	0.0	0	0.0	0	0.0	1	10.0
URINARY BLADDER	# EX	10		0		0		10	
Inflammation, chronic		1	10.0	0	0.0	0	0.0	0	0.0
URETER	# EX	10		0		0		10	
PROSTATE	# EX	10		0		0		9	
SKIN	# EX	10		0		0		10	
MAMMARY GLAND	# EX	2		0		0		2	
ILEUM	# EX	10		0		0		10	
CECUM	# EX	10		0		0		10	

Incidence Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

PROJECT SUMMARY

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL

SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1 (1)		2 (2)		3 (3)		4 (4)	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
LYMPH NODE, MESENTERIC	# EX	10		0		0		9	
TESTES	# EX	10		0		0		10	
EPIDIDYMIS	# EX	10		0		0		10	
TONGUE	# EX	10		0		0		10	
PANCREAS	# EX	10		0		0		10	
Vacuolation, multifocal		1	10.0	0	0.0	0	0.0	0	0.0
SKELETAL MUSCLE	# EX	10		0		0		10	
SCIATIC NERVE	# EX	10		0		0		10	
FEMUR WITH MARROW	# EX	10		0		0		10	
EYE	# EX	10		0		0		10	
HARDERIAN GLAND	# EX	10		0		0		10	

Incidence Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

PROJECT SUMMARY

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL

SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1 (1)		2 (2)		3 (3)		4 (4)	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
BRAIN	# EX	10		0		0		10	
Meningioma		0	0.0	0	0.0	0	0.0	1	10.0
PITUITARY GLAND	# EX	10		0		0		8	
THYMUS	# EX	10		0		0		10	
Hemorrhage, focal		1	10.0	0	0.0	0	0.0	0	0.0
SALIVARY GLAND	# EX	10		0		0		10	
Inflammation, chronic		0	0.0	0	0.0	0	0.0	1	10.0
SPINAL CORD (THORACIC)	# EX	10		0		0		10	
ADRENAL GLAND	# EX	10		0		0		10	
Ectopic acirenal		2	20.0	0	0.0	0	0.0	0	0.0
Hyperplasia, spindle cell		10	100.0	0	0.0	0	0.0	9	90.0
THYROID GLAND	# EX	10		0		0		10	
PARATHYROID GLAND	# EX	9		0		0		7	
Cyst		1	11.0	0	0.0	0	0.0	0	0.0
TRACHEA	# EX	10		0		0		10	
ESOPHAGUS	# EX	10		0		0		10	
HEART	# EX	10		0		0		10	
DUODENUM	# EX	10		0		0		10	

Incidence Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

DRAFT

PROJECT SUMMARY

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL
SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1 (1)		2 (2)		3 (3)		4 (4)	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
COLON	# EX	10		0		0		10	
STOMACH	# EX	10		0		0		10	
Inflammation, subacute, glandular mucosa		0	0.0	0	0.0	0	0.0	1	10.0
LIVER	# EX	10		10		10		10	
Depletion, glycogen		2	20.0	2	20.0	1	10.0	8	80.0
Inflammation, chronic, multifocal		5	50.0	0	0.0	0	0.0	2	20.0
Necrosis, individual cell		0	0.0	0	0.0	0	0.0	2	20.0
GALLBLADDER	# EX	10		0		0		10	
SPLEEN	# EX	10		0		0		10	
JEJUNUM	# EX	10		0		0		10	
LUNG	# EX	10		0		0		10	
Inflammation, chronic, peribronchial		1	10.0	0	0.0	0	0.0	0	0.0
KIDNEY	# EX	10		10		10		10	
Inflammation, chronic, cortex		1	10.0	3	30.0	3	30.0	1	10.0
Nephropathy		0	0.0	0	0.0	0	0.0	1	10.0
URINARY BLADDER	# EX	10		0		0		9	
Inflammation, chronic		1	10.0	0	0.0	0	0.0	2	22.0
URETER	# EX	10		0		0		10	
SKIN	# EX	10		0		0		10	

Incidence Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

DRAFT

PROJECT SUMMARY

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL
SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		1 (1)		2 (2)		3 (3)		4 (4)	
NUMBER OF ANIMALS:		10		10		10		10	
		#	%	#	%	#	%	#	%
MAMMARY GLAND	# EX	10		0		0		10	
ILEUM	# EX	10		0		0		10	
CECUM	# EX	10		0		0		10	
LYMPH NODE, MESENTERIC	# EX	10		0		0		9	
OVARY	# EX	10		0		0		9	
UTERUS	# EX	10		0		0		10	
VAGINA	# EX	10		0		0		10	
TONGUE	# EX	10		0		0		10	
Inflammation, chronic		1	10.0	0	0.0	0	0.0	0	0.0
PANCREAS	# EX	10		0		0		10	
SKELETAL MUSCLE	# EX	10		0		0		10	
SCIATIC NERVE	# EX	9		0		0		10	
FEMUR WITH MARROW	# EX	10		0		0		10	
EYE	# EX	10		0		0		10	
HARDERIAN GLAND	# EX	10		0		0		10	

Incidence Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

SECTION III

SEVERITY SUMMARY TABLE

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

SEVERITY SUMMARY

DRAFT

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL
SEX: MALE

GROUP:		1 (1)	2 (2)	3 (3)	4 (4)
NUMBER OF ANIMALS:		10	10	10	10
		# SEV	# SEV	# SEV	# SEV
BRAIN	# EX	10	0	0	10
PITUITARY GLAND	# EX	9	0	0	8
THYMUS	# EX	10	10	10	10
Hemorrhage, focal		0 0.00	1 0.10	0 0.00	2 0.20
SALIVARY GLAND	# EX	10	0	0	10
SPINAL CORD (THORACIC)	# EX	10	0	0	10
ADRENAL GLAND	# EX	10	0	0	10
Ectopic adrenal		0 0.00	0 0.00	0 0.00	1 0.20
THYROID GLAND	# EX	10	0	0	10
PARATHYROID GLAND	# EX	9	0	0	9
Cyst		1 0.22	0 0.00	0 0.00	0 0.00
TRACHEA	# EX	10	0	0	10
ESOPHAGUS	# EX	10	0	0	10
HEART	# EX	10	0	0	10
DUODENUM	# EX	10	0	0	10
COLON	# EX	10	0	0	10
STOMACH	# EX	10	0	0	10
Cyst, glandular mucosa		1 0.10	0 0.00	0 0.00	0 0.00

Severity Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

SEVERITY SUMMARY

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL

SEX: MALE

GROUP:		1 (1)		2 (2)		3 (3)		4 (4)	
NUMBER OF ANIMALS:		10		10		10		10	
		#	SEV	#	SEV	#	SEV	#	SEV
LIVER	# EX	10		10		10		10	
Depletion, glycogen		8	1.00	8	0.90	10	1.10	10	1.90
GALLBLADDER	# EX	10		0		0		9	
SPLEEN	# EX	10		0		0		10	
JEJUNUM	# EX	10		0		0		10	
LUNG	# EX	10		0		0		10	
Inflammation, chronic, peribronchial		0	0.00	0	0.00	0	0.00	1	0.10
KIDNEY	# EX	10		10		10		10	
Inflammation, chronic, cortex		1	0.10	1	0.10	1	0.10	4	0.40
Nephropathy		0	0.00	0	0.00	0	0.00	1	0.10
URINARY BLADDER	# EX	10		0		0		10	
Inflammation, chronic		1	0.10	0	0.00	0	0.00	0	0.00
URETER	# EX	10		0		0		10	
PROSTATE	# EX	10		0		0		9	
SKIN	# EX	10		0		0		10	
MAMMARY GLAND	# EX	2		0		0		2	
ILEUM	# EX	10		0		0		10	
CECUM	# EX	10		0		0		10	

Severity Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

SEVERITY SUMMARY

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL
SEX: MALE

GROUP:		1 (1)		2 (2)		3 (3)		4 (4)	
NUMBER OF ANIMALS:		10		10		10		10	
		#	SEV	#	SEV	#	SEV	#	SEV
LYMPH NODE, MESENTERIC	# EX	10		0		0		9	
TESTES	# EX	10		0		0		10	
EPIDIDYMIS	# EX	10		0		0		10	
TONGUE	# EX	10		0		0		10	
PANCREAS	# EX	10		0		0		10	
Vacuolation, multifocal		1	0.20	0	0.00	0	0.00	0	0.00
SKELETAL MUSCLE	# EX	10		0		0		10	
SCIATIC NERVE	# EX	10		0		0		10	
FEMUR WITH MARROW	# EX	10		0		0		10	
EYE	# EX	10		0		0		10	
HARDERIAN GLAND	# EX	10		0		0		10	

Severity Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

SEVERITY SUMMARY

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL
SEX: FEMALE

GROUP:		1 (1)		2 (2)		3 (3)		4 (4)	
NUMBER OF ANIMALS:		10		10		10		10	
		#	SEV	#	SEV	#	SEV	#	SEV
BRAIN	# EX	10		0		0		10	
PITUITARY GLAND	# EX	10		0		0		8	
THYMUS	# EX	10		0		0		10	
Hemorrhage, focal		1	0.10	0	0.00	0	0.00	0	0.00
SALIVARY GLAND	# EX	10		0		0		10	
Inflammation, chronic		0	0.00	0	0.00	0	0.00	1	0.10
SPINAL CORD (THORACIC)	# EX	10		0		0		10	
ADRENAL GLAND	# EX	10		0		0		10	
Ectopic adrenal		2	0.20	0	0.00	0	0.00	0	0.00
Hyperplasia, spindle cell		10	1.10	0	0.00	0	0.00	9	1.00
THYROID GLAND	# EX	10		0		0		10	
PARATHYROID GLAND	# EX	9		0		0		7	
Cyst		1	0.11	0	0.00	0	0.00	0	0.00
TRACHEA	# EX	10		0		0		10	
ESOPHAGUS	# EX	10		0		0		10	
HEART	# EX	10		0		0		10	
DUODENUM	# EX	10		0		0		10	
COLON	# EX	10		0		0		10	

Severity Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

SEVERITY SUMMARY

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL
SEX: FEMALE

GROUP:		1 (1)		2 (2)		3 (3)		4 (4)	
NUMBER OF ANIMALS:		10		10		10		10	
		#	SEV	#	SEV	#	SEV	#	SEV
STOMACH	# EX	10		0		0		10	
Inflammation, subacute, glandular mucosa		0	0.00	0	0.00	0	0.00	1	0.20
LIVER	# EX	10		10		10		10	
Depletion, glycogen		2	0.20	2	0.20	1	0.10	8	1.30
Inflammation, chronic, multifocal		5	0.50	0	0.00	0	0.00	2	0.20
Necrosis, individual cell		0	0.00	0	0.00	0	0.00	2	0.20
GALLBLADDER	# EX	10		0		0		10	
SPLEEN	# EX	10		0		0		10	
JEJUNUM	# EX	10		0		0		10	
LUNG	# EX	10		0		0		10	
Inflammation, chronic, peribronchial		1	0.10	0	0.00	0	0.00	0	0.00
KIDNEY	# EX	10		10		10		10	
Inflammation, chronic, cortex		1	0.10	3	0.30	3	0.30	1	0.10
Nephropathy		0	0.00	0	0.00	0	0.00	1	0.10
URINARY BLADDER	# EX	10		0		0		9	
Inflammation, chronic		1	0.10	0	0.00	0	0.00	2	0.22
URETER	# EX	10		0		0		10	
SKIN	# EX	10		0		0		10	
MAMMARY GLAND	# EX	10		0		0		10	
ILEUM	# EX	10		0		0		10	

Severity Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

SEVERITY SUMMARY

STUDY ID : TRL STUDY NUMBER 166 STUDY NUMBER: SN166
FATE: ALL
SEX: FEMALE

GROUP:		1 (1)		2 (2)		3 (3)		4 (4)	
NUMBER OF ANIMALS:		10		10		10		10	
		#	SEV	#	SEV	#	SEV	#	SEV
CECUM	# EX	10		0		0		10	
LYMPH NODE, MESENTERIC	# EX	10		0		0		9	
OVARY	# EX	10		0		0		9	
UTERUS	# EX	10		0		0		10	
VAGINA	# EX	10		0		0		10	
TONGUE	# EX	10		0		0		10	
Inflammation, chronic		1	0.10	0	0.00	0	0.00	0	0.00
PANCREAS	# EX	10		0		0		10	
SKELETAL MUSCLE	# EX	10		0		0		10	
SCIATIC NERVE	# EX	9		0		0		10	
FEMUR WITH MARROW	# EX	10		0		0		10	
EYE	# EX	10		0		0		10	
HARDERIAN GLAND	# EX	10		0		0		10	

Severity Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day
(2) - 1 mg/kg/day
(3) - 5 mg/kg/day
(4) - 25 mg/kg/day

SECTION IV

TABULATED ANIMAL DATA

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 1: 0 mg/kg/day
SEX: MALE

ANIMAL ID:	0201	0202	0203	0204	0205	0206	0207	0208	0209	0210
BRAIN	N	N	N	N	N	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N	N	N	U	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N
SALIVARY GLAND	N	N	N	N	N	N	N	N	N	N
SPINAL CORD (THORACIC)	N	N	N	N	N	N	N	N	N	N
ADRENAL GLAND	N	N	N	N	N	N	N	N	N	N
THYROID GLAND	N	N	N	N	N	N	N	N	N	N
PARATHYROID GLAND	N	N	N	N	U	N		N	N	N
Cyst	-	-	-	-	-	-	2	-	-	-
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
HEART	N	N	N	N	N	N	N	N	N	N
DUODENUM	N	N	N	N	N	N	N	N	N	N
COLON	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N		N	N	N	N
Cyst, glandular mucosa	-	-	-	-	-	1	-	-	-	-
LIVER			N				N			
Depletion, glycogen	1	1	-	1	2	1	-	1	2	1

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166 — STUDY NUMBER: SN166
FATE: ALL — GROUP: 1: 0 mg/kg/day
SEX: MALE

ANIMAL ID:	0201	0202	0203	0204	0205	0206	0207	0208	0209	0210
GALLBLADDER	N	N	N	N	N	N	N	N	N	N
SPLEEN	N	N	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N	N	N
LUNG	N	N	N	N	N	N	N	N	N	N
KIDNEY	N		N	N	N	N	N	N	N	N
Inflammation, chronic, cortex	-	1	-	-	-	-	-	-	-	-
URINARY BLADDER	N	N	N	N	N		N	N	N	N
Inflammation, chronic	-	-	-	-	-	1	-	-	-	-
URETER	N	N	N	N	N	N	N	N	N	N
PROSTATE	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
MAMMARY GLAND	U	U	N	N	U	U	U	U	U	U
ILEUM	N	N	N	N	N	N	N	N	N	N
CECUM	N	N	N	N	N	N	N	N	N	N
LYMPH NODE, MESENTERIC	N	N	N	N	N	N	N	N	N	N
TESTES	N	N	N	N	N	N	N	N	N	N
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N
TONGUE	N	N	N	N	N	N	N	N	N	N
PANCREAS	N		N	N	N	N	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 1: 0 mg/kg/day
SEX: MALE

ANIMAL ID:	0201	0202	0203	0204	0205	0206	0207	0208	0209	0210
PANCREAS	N		N	N	N	N	N	N	N	N
Vacuolation, multifocal	-	2	-	-	-	-	-	-	-	-
SKELETAL MUSCLE	N	N	N	N	N	N	N	N	N	N
SCIATIC NERVE	N	N	N	N	N	N	N	N	N	N
FEMUR WITH MARROW	N	N	N	N	N	N	N	N	N	N
EYE	N	N	N	N	N	N	N	N	N	N
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166 — STUDY NUMBER: SN166
FATE: ALL — GROUP: 2: 1 mg/kg/day
SEX: MALE

ANIMAL ID:	0221	0222	0223	0224	0225	0226	0227	0228	0229	0230
THYMUS	N	N	N	N	N	N		N	N	N
Hemorrhage, focal	-	-	-	-	-	-	1	-	-	-
LIVER			N					N		
Depletion, glycogen	1	1	-	2	1	1	1	-	1	1
KIDNEY	N	N	N	N	N	N	N		N	N
Inflammation, chronic, cortex	-	-	-	-	-	-	-	1	-	-

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 3: 5 mg/kg/day
SEX: MALE

ANIMAL ID:	0241	0242	0243	0244	0245	0246	0247	0248	0249	0250
THYMUS	N	N	N	N	N	N	N	N	N	N
LIVER										
Depletion, glycogen	1	1	1	1	1	2	1	1	1	1
KIDNEY	N	N	N	N	N	N	N	N	N	
Inflammation, chronic, cortex	-	-	-	-	-	-	-	-	-	1

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

DRAFT

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 4: 25 mg/kg/day
SEX: MALE

ANIMAL ID:	0261	0262	0263	0264	0265	0266	0267	0268	0269	0270
SPLEEN	N	N	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N	N	N
LUNG	N	N	N	N	N	N	N	N		N
Inflammation, chronic, peribronchial	-	-	-	-	-	-	-	-	1	-
KIDNEY			N	N				N	N	N
Inflammation, chronic, cortex	1	1	-	-	-	1	1	-	-	-
Nephropathy	-	-	-	-	1	-	-	-	-	-
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N
URETER	N	N	N	N	N	N	N	N	N	N
PROSTATE	N	N	N	N	N	N	N	U	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
MAMMARY GLAND	U	N	U	U	U	U	U	N	U	U
ILEUM	N	N	N	N	N	N	N	N	N	N
CECUM	N	N	N	N	N	N	N	N	N	N
LYMPH NODE, MESENTERIC	N	N	N	N	N	N	N	U	N	N
TESTES	N	N	N	N	N	N	N	N	N	N
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N
TONGUE	N	N	N	N	N	N	N	N	N	N
PANCREAS	N	N	N	N	N	N	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

DRAFT

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 4: 25 mg/kg/day
SEX: MALE

ANIMAL ID:	0261	0262	0263	0264	0265	0266	0267	0268	0269	0270
SKELETAL MUSCLE	N	N	N	N	N	N	N	N	N	N
SCIATIC NERVE	N	N	N	N	N	N	N	N	N	N
FEMUR WITH MARROW	N	N	N	N	N	N	N	N	N	N
EYE	N	N	N	N	N	N	N	N	N	N
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 1: 0 mg/kg/day
SEX: FEMALE

ANIMAL ID:	0211	0212	0213	0214	0215	0216	0217	0218	0219	0220
BRAIN	N	N	N	N	N	N	N	N	N	N
PITUITARY GLAND	N	N	N	N	N	N	N	N	N	N
THYMUS	N	N	N	N	N	N	N	N		N
Hemorrhage, focal	-	-	-	-	-	-	-	-	1	-
SALIVARY GLAND	N	N	N	N	N	N	N	N	N	N
SPINAL CORD (THORACIC)	N	N	N	N	N	N	N	N	N	N
ADRENAL GLAND										
Ectopic adrenal	-	-	-	-	-	-	-	1	1	-
Hyperplasia, spindle cell	1	1	1	1	1	1	2	1	1	1
THYROID GLAND	N	N	N	N	N	N	N	N	N	N
PARATHYROID GLAND		N	N	N	N	N	U	N	N	N
Cyst	1	-	-	-	-	-	-	-	-	-
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
HEART	N	N	N	N	N	N	N	N	N	N
DUODENUM	N	N	N	N	N	N	N	N	N	N
COLON	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER		N	N	N	N				N	
Depletion, glycogen	-	-	-	-	-	1	-	1	-	-
Inflammation, chronic, multifocal	1	-	-	-	-	1	1	1	-	1

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 1: 0 mg/kg/day
SEX: FEMALE

ANIMAL ID:	0211	0212	0213	0214	0215	0216	0217	0218	0219	0220
GALLBLADDER	N	N	N	N	N	N	N	N	N	N
SPLEEN	N	N	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N	N	N
LUNG	N	N		N	N	N	N	N	N	N
Inflammation, chronic, peribronchial	-	-	1	-	-	-	-	-	-	-
KIDNEY	N	N	N	N	N	N	N	N		N
Inflammation, chronic, cortex	-	-	-	-	-	-	-	-	1	-
URINARY BLADDER	N	N	N	N	N	N	N		N	N
Inflammation, chronic	-	-	-	-	-	-	-	1	-	-
URETER	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N
ILEUM	N	N	N	N	N	N	N	N	N	N
CECUM	N	N	N	N	N	N	N	N	N	N
LYMPH NODE, MESENTERIC	N	N	N	N	N	N	N	N	N	N
OVARY	N	N	N	N	N	N	N	N	N	N
UTERUS	N	N	N	N	N	N	N	N	N	N
VAGINA	N	N	N	N	N	N	N	N	N	N
TONGUE	N	N	N	N	N	N	N	N		N
Inflammation, chronic	-	-	-	-	-	-	-	-	1	-

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 1: 0 mg/kg/day
SEX: FEMALE

ANIMAL ID:	0211	0212	0213	0214	0215	0216	0217	0218	0219	0220
PANCREAS	N	N	N	N	N	N	N	N	N	N
SKELETAL MUSCLE	N	N	N	N	N	N	N	N	N	N
SCIATIC NERVE	N	U	N	N	N	N	N	N	N	N
FEMUR WITH MARROW	N	N	N	N	N	N	N	N	N	N
EYE	N	N	N	N	N	N	N	N	N	N
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 2: 1 mg/kg/day
SEX: FEMALE

ANIMAL ID:	0231	0232	0233	0234	0235	0236	0237	0238	0239	0240
LIVER	N		N	N	N		N	N	N	N
Depletion, glycogen	-	1	-	-	-	1	-	-	-	-
KIDNEY	N	N	N	N	N			N		N
Inflammation, chronic, cortex	-	-	-	-	-	1	1	-	1	-

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 3: 5 mg/kg/day
SEX: FEMALE

ANIMAL ID:	0251	0252	0253	0254	0255	0256	0257	0258	0259	0260
LIVER		N	N	N	N	N	N	N	N	N
Depletion, glycogen	1	-	-	-	-	-	-	-	-	-
KIDNEY	N			N	N		N	N	N	N
Inflammation, chronic, cortex	-	1	1	-	-	1	-	-	-	-

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 4: 25 mg/kg/day
SEX: FEMALE

ANIMAL ID:	0271	0272	0273	0274	0275	0276	0277	0278	0279	0280
BRAIN	N	N	N	N	N	N	N	N		N
Meningioma	-	-	-	-	-	-	-	-	B	-
PITUITARY GLAND	N	N	N	N	N	U	U	N	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N
SALIVARY GLAND	N	N	N	N	N		N	N	N	N
Inflammation, chronic	-	-	-	-	-	1	-	-	-	-
SPINAL CORD (THORACIC)	N	N	N	N	N	N	N	N	N	N
ADRENAL GLAND					N					
Hyperplasia, spindle cell	1	1	2	1	-	1	1	1	1	1
THYROID GLAND	N	N	N	N	N	N	N	N	N	N
PARATHYROID GLAND	N	N	U	N	U	N	U	N	N	N
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
HEART	N	N	N	N	N	N	N	N	N	N
DUODENUM	N	N	N	N	N	N	N	N	N	N
COLON	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N		N	N	N	N	N	N
Inflammation, subacute, glandular mucosa	-	-	-	2	-	-	-	-	-	-
LIVER	N								N	
Depletion, glycogen	-	1	1	2	2	1	2	2	-	2
Inflammation, chronic, multifocal	-	1	1	-	-	-	-	-	-	-

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166 — STUDY NUMBER: SN166
FATE: ALL — GROUP: 4: 25 mg/kg/day
SEX: FEMALE

ANIMAL ID:	0271	0272	0273	0274	0275	0276	0277	0278	0279	0280
LIVER	N								N	
Necrosis, individual cell	-	1	1	-	-	-	-	-	-	-
GALLBLADDER	N	N	N	N	N	N	N	N	N	N
SPLEEN	N	N	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N	N	N
LUNG	N	N	N	N	N	N	N	N	N	N
KIDNEY	N	N	N	N	N	N			N	N
Inflammation, chronic, cortex	-	-	-	-	-	-	1	-	-	-
Nephropathy	-	-	-	-	-	-	-	1	-	-
URINARY BLADDER		N	N		U	N	N	N	N	N
Inflammation, chronic	1	-	-	1	-	-	-	-	-	-
URETER	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N
ILEUM	N	N	N	N	N	N	N	N	N	N
CECUM	N	N	N	N	N	N	N	N	N	N
LYMPH NODE, MESENTERIC	N	N	N	N	N	N	N	N	U	N
OVARY	N	N	N	N	U	N	N	N	N	N
UTERUS	N	N	N	N	N	N	N	N	N	N
VAGINA	N	N	N	N	N	N	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
THREE MONTH ORAL (GAVAGE) TOXICITY STUDY
OF HALOFANTRINE HYDROCHLORIDE IN MICE
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 166

DRAFT

TABULATED ANIMAL DATA

STUDY ID : TRL STUDY NUMBER 166
FATE: ALL

STUDY NUMBER: SN166
GROUP: 4: 25 mg/kg/day
SEX: FEMALE

ANIMAL ID:	0271	0272	0273	0274	0275	0276	0277	0278	0279	0280
TONGUE	N	N	N	N	N	N	N	N	N	N
PANCREAS	N	N	N	N	N	N	N	N	N	N
SKELETAL MUSCLE	N	N	N	N	N	N	N	N	N	N
SCIATIC NERVE	N	N	N	N	N	N	N	N	N	N
FEMUR WITH MARROW	N	N	N	N	N	N	N	N	N	N
EYE	N	N	N	N	N	N	N	N	N	N
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N

See Reports Code Table for Symbol Definitions

APPENDIX 12

PROTOCOL AND PROTOCOL AMENDMENTS

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-11B
Study No.: 166

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

1.0 PURPOSE OF THE STUDY:

The purpose of this study is to determine the oral toxicity of halofantrine hydrochloride in B6C3F1 mice following thirteen weeks of daily administration by gavage. This study will be conducted in accordance with the specifications of the Sponsor as described in Task Order UIC-11. The protocol for this study was approved by the UIC Animal Care Committee (Appendix 1).

2.0 SPONSOR:

2.1	Name:	U.S. Army Medical Materiel Development Activity
2.2	Address:	Fort Detrick Frederick, MD 21702-5009
2.3	Representative:	George J. Schieferstein, Ph.D.

3.0 TESTING FACILITY:

3.1	Name:	Toxicology Research Laboratory (TRL)
3.2	Address:	University of Illinois at Chicago (UIC) Department of Pharmacology 1940 W. Taylor St. Chicago, IL 60612-7353
3.3	Study Director:	Barry S. Levine, D.Sc., D.A.B.T.

4.0 DATES:

4.1	Proposed Initiation of Dosing:	02/16/95
4.2	Proposed Necropsy Dates:	05/18-19/95
4.3	Proposed Study Completion Date (Draft Study Report):	08/18/95

5.0 TEST ARTICLE

5.1	Name or Code No:	Halofantrine HCl (WR171669)

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5.2 TRL Chemical No: 1950614

5.3 Physical Description: White powder

5.4 Stability and Handling of Test Article:

5.4.1 Storage Conditions to Maintain Stability:

5.4.1.1 Temperature: Room temperature

5.4.1.2 Humidity: Ambient conditions at room temperature

5.4.1.3 Light: No requirements

5.4.1.4 Special Requirements: None

5.4.2 Special Handling Procedures: Standard safety precautions including gloves, eye protection, mask, and lab coats.

5.4.3 Log of Test Article: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, all unused test article will be returned to the Sponsor if requested.

6.0 PERSONNEL:

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Toxicologist	Clyde W. Wheeler, Ph.D.
Pathologist	Robert L. Morrissey, D.V.M., Ph.D., D.A.C.V.P.
Analytical Chemist	Adam Negrusz, Ph.D.
Clinical Veterinarian	James E. Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Ophthalmologist	Samuel J. Vainisi, D.V.M., D.A.C.V.O.
Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	To be documented in the raw data
Clinical Pathology	Maria Lang, A.H.T., C.V.T.
Quality Assurance	Ronald C. Schoenbeck

7.0 TEST SYSTEM:

7.1 Species: Mouse

7.2 Strain: B6C3F1 (Virus Antibody Free)

7.3 Number and Sex: 40 Males and 40 Females

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7.4 Age of Animals: Approximately 6-7 weeks old at dosing initiation.

7.5 Weight of Animals: Approximately 22 - 26 g (males) and approximately 18 - 22 g (females) at dosing initiation.

7.6 Source of Animals: Charles River Breeding Laboratories. The specific breeding facility will be documented in the raw data.

7.7 Justification for Selection of Test System: This study is being conducted to select dose levels for a carcinogenicity study. The mouse is a standard and accepted rodent species for carcinogenicity studies, and is specified by the Sponsor.

7.8 Procedure for Unique Identification of Test System: Upon arrival, each animal will be given a study-unique quarantine/pretest number. During the animal selection process, each animal will be assigned an animal number unique to it within the population making up the study. This number will appear as an ear tag and will also be coded on a subcutaneously implanted microchip. It will also appear on a cage card visible on the front of each cage. The cage card will additionally contain the study number, test article identification, treatment group number and dose level. Cage cards will be color-coded as a function of treatment group. Raw data records and specimens will also be identified by the unique test animal number.

7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be singly housed in polycarbonate cages with Anderson bed-o-cob bedding (Heinhold, Kankakee, IL) in a temperature (65-78°F) and humidity (approx. 30-70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size will be adequate to house mice at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHEW (NIH) No. 86-23. All animals will be routinely transferred to clean cages once weekly.

7.10 Quarantine Procedure: Animals will be quarantined for approximately one week. During that time, the animals will be observed daily for signs of illness or death, and all unusual observations will be reported to the Study Director, Toxicologist or Clinical Veterinarian. Animals will be examined during quarantine and approved for use by the Clinical Veterinarian prior to being placed on test. Any sickly animals will be eliminated prior to the test animal selection process. If a selected animal appears sickly prior to initiation of treatment, it will be replaced by a healthy animal prior to initiation of treatment under the direction of the Study Director or Toxicologist. Quarantine release will be documented by the veterinarian prior to study initiation.

7.11 Food: Certified Rodent Chow No. 5002 (PMI Feeds, Inc. St. Louis, MO) will be provided *ad libitum* from arrival until termination.

7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is not treated with additional chlorine or HCl.

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7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of bimonthly comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

7.14 It is not known if the animals will experience pain or distress during the study. Analgesic or anesthetic agents will confound the ability to determine the toxic potential of the test article, and therefore will not be used. If an animal is in severe pain or distress, following consultation with the veterinary staff, it will be euthanized in accordance with standard operating procedures.

8.0 EXPERIMENTAL DESIGN:

8.1 Treatment Groups:

Treatment Group	Dose Level (mg/kg/day)	Number of Males	Number of Females
1	0	10	10
2	1	10	10
3	5	10	10
4	25	10	10

Dose levels are determined from a 4 week oral dose range-finding study in mice.

8.2 Frequency and Route of Administration of the Test Article: The test article will be administered by gavage once daily for at least 13 weeks. Control animals will receive the test article vehicle. To acclimate them to the procedure, all animals will receive vehicle by gavage for the 3 days immediately prior to the first day of dosing. All animals will be dosed up to and including the day prior to their scheduled necropsy. Dosing volume will be 10 ml/kg, adjusted on the basis of each animal's most recent body weight. The actual volume (ml) administered will be documented in the raw data.

8.3 Justification of Route(s): Oral treatment is the intended clinical route of administration and is specified by the Sponsor.

8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: During the quarantine/pretest period, the animals will be randomized by sex into the four groups shown in Section 8.1 using a computer-generated randomization procedure on the basis of body weight.

8.5 Test Article Vehicle: 0.5% Aqueous methylcellulose

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8.6 Test Article Dosage Form Preparation and Analyses: The test and control materials will be assumed to be 100% pure for dosing calculations. Formulations will be prepared at least weekly and will be administered daily by gavage, at 10 ml/kg/day, 7 days a week. Since no adjustment for purity will be made, suspensions will be prepared on the basis of weight of the salt, halofantrine hydrochloride. The methylcellulose vehicle will be prepared at least weekly by placing the required amount of deionized water in a beaker and then adding the required amount of methylcellulose which will be weighed on an analytical balance (0.5 g of methylcellulose per 100 ml of deionized water). One lot no. of methylcellulose will be used for the 4 and 13 week studies. The mixture will be stirred until homogeneous and then refrigerated.

Each test article dosing suspension will be prepared individually by adding the appropriate amount of halofantrine with approximately one-third to one-half of the required 0.5% methylcellulose vehicle in a pre-calibrated beaker. The contents will be mixed with an Omni-Mixer homogenizer, for at least 2 minutes. The mixture will then be brought to the final volume using vehicle and again mixed for an additional 2 - 5 minutes. All suspensions will be stored at 2 - 8°C. All suspensions will be allowed to warm to room temperature and stirred continuously before and during gavage administration. Dosing suspensions prepared for use in weeks 1, 3, 7, 10 and 13 will be analyzed, and only suspensions within 10% of their target concentration will be used. Approximately 10 ml from all dosing suspensions will be reserved, frozen and retained for possible analysis.

8.7 Type and Frequency of Observations, Tests, Analyses and Measurements:

8.7.1 Mortality Check: All animals will be observed for moribundity/mortality immediately prior to dosing in the morning and in the afternoon.

8.7.2 Clinical Signs: All animals will be observed for clinical signs of toxicity approximately 1 - 2 hours after dosing.

8.7.3 Clinical Observations: All animals will be subjected to a physical examination including examination of eyes and all orifices once weekly starting in Week -1.

8.7.4 Body Weight: Body weights of all animals will be recorded weekly starting in Week -1 and at scheduled necropsy.

8.7.5 Food Consumption: Food consumption for all animals will be measured weekly starting in Week -1.

8.7.6 Ophthalmologic Examinations: All mice will be examined by indirect ophthalmoscopy prior to study initiation and in Week 13.

8.7.7 Clinical Pathology: At necropsy, hematology parameters will be measured in one-half the animals (5 animals/sex/group) and clinical chemistry parameters will be measured in the remaining animals (5 animals/sex/group). For the "hematology" animals, blood for serum harvest will also be collected. If necessary, this serum will be used to complete the battery of clinical chemistry tests. The non-fasted animals will be anesthetized by carbon dioxide inhalation

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(CO_2/O_2:80%/20%) and approximately 0.5 - 0.75 ml of blood will be collected from the orbital sinus to measure the following parameters. The samples will be processed in the same random order as collected.

Hematology

[a]Erythrocyte count and morphology	Mean corpuscular volume(MCV)
Hematocrit	Mean corpuscular hemoglobin (MCH)
Hemoglobin	Mean corpuscular hemoglobin concentration (MCHC)
Leukocyte count, total and differential	Platelet count
	Reticulocyte count

[a]Includes nucleated RBCs.

Clinical Chemistry

The clinical chemistry tests will be prioritized as shown on the basis of the sample volume obtained.

(1) Thyroid stimulating hormone (TSH)[a]	(8) Sorbitol dehydrogenase (SDH)
(2) Alanine aminotransferase (ALT)	(9) Total protein
(3) Alkaline phosphatase	(10) Albumin (A)
(4) Cholesterol	(11) Globulin (G) (calc.)
(5) Glucose	(12) A/G ratio (calc.)
(6) BUN	(13) Total bile acids
(7) Triglycerides	(14) Inorganic phosphorus

[a]Serum will be frozen at -70°C and shipped to Anilytics Incorporated (Gaithersburg, MD) for the measurement of TSH levels. The analysis will be performed under GLP regulations.

8.7.8 Pathology: All animals which die on test or are sacrificed if moribund will be necropsied on that day. Surviving animals will be sacrificed and necropsied over a two consecutive day period following 13 week of treatment. Euthanasia will be accomplished by carbon dioxide asphyxiation (CO_2/O_2:80%/20%) and an extensive necropsy will be performed under the direction and supervision of the pathologist. Terminal body weights will be collected prior to routine sacrifice. The necropsy procedure will be a thorough and systematic examination and dissection of the animal viscera and carcass, and collection and fixation of the following tissues/organs in 10% neutral buffered formalin. The ear with its attached identification tag will be saved with the wet tissues.

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Adrenal glands	Ovaries
*Brain	Pancreas
Cecum	Pituitary
Colon	Prostate
Duodenum	Salivary gland (submaxillary)
Epididymides	Sciatic nerve
Esophagus	Skeletal muscle
Eyes with harderian glands	Skin (abdominal) with Mammary gland
Femur with marrow	Spinal cord (thoracic)
Gall bladder	*Spleen
Gross lesions	Stomach
*Heart	*Testes
Ileum	Thymus
Jejunum	Thyroid gland/Parathyroids
*Kidneys	Tongue
*Liver	Trachea
*Lungs/Bronchi	Ureter
Lymph node (mesenteric)	Urinary bladder
	Uterus
	Vagina

*Weighed at scheduled necropsy. Paired organs will be weighed as a unit.

All tissues and organs collected at necropsy will be examined microscopically for all control and high dose animals. If treatment-related lesions are seen, those tissues will be examined microscopically in low and mid dose animals. Gross lesions will be examined microscopically in all animals.

8.7.9 Statistical Analyses: For each sex, Analysis of Variance tests will be conducted on body weight, weight gains, food consumption, hematology, clinical chemistry and organ weight data. Organ weight analysis will consider weights relative to brain weight. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's t test will be used for pair-wise comparisons to the control group. Frequency data such as incidence or mortality, gross necropsy observations and tissue morphology observations will be compared by Fishers Exact Test or Chi-square analyses as necessary.

Quantitative data will be tabulated and presented in the report. In addition to the written report, summary data tables of parameters and variability will be transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk will no longer be considered GLP compliant.

9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct study, except those that are generated as direct computer input, shall be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that shall be bound during or at the conclusion of the nonclinical laboratory study. All appropriate computer and machine output shall be bound during or at the conclusion of the study. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data. Any changes in entries for whatever reason (e.g., to correct an error or transposition) shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of data input. In computer driven collection systems, the operator responsible for direct input shall be identified at the time of data input. Any changes in computer entries for whatever reason (e.g, to correct an error or transposition) shall be made in such manner so as not to obscure the original entry, if possible, shall indicate the reason for such change, and shall be dated and the responsible individual shall be identified.

All recorded data shall be reviewed, signed. and dated by a knowledgeable person, other than the person making the entry, to assure adherence to procedures and to verify observations.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens, test article reserves and other materials necessary to reconstruct the study will be stored in the TRL archives maintained by Quality Assurance, unless specified by the Sponsor.

All changes or revisions. and reasons therefore, to this protocol once it is approved shall be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol.

10.0 REGULATORY REQUIREMENTS:

This study will be performed in compliance with the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards.

Will this study be submitted to a regulatory agency? Yes
If so, to which agency(ies)? U.S. Food and Drug Administration
Does the Sponsor request that test article samples be returned? Possibly: direction will be provided by the Sponsor
Does the Sponsor request that samples of the test article/carrier mixture(s) be returned to the Sponsor? No

11.0 PROTOCOL APPROVAL:

STUDY DIRECTOR: _____ 8/26/94
Barry S. Levine, D.Sc., D.A.B.T. Date

QUALITY ASSURANCE: _____ 8/26/94
Ronald Schoenbeck Date

SPONSOR APPROVAL: _____ 8/29/94
George Schieferstein, Ph.D. Date
Contracting Officer's
Representative (COR)

COMMENTS FROM THE COR:

UIC The University of Illinois at Chicago

DRAFT

Office of the Vice Chancellor for Research (M/C 672)
310 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227
(312) 996-4995

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-11B
Study No.: 166

APPENDIX 1

August 23, 1994

Barry S. Levine
Pharmacology
312 BGRC, M/C 868

Dear Dr. Levine:

The modifications requested in your correspondence of August 19, 1994 pertaining to your approved protocol ACC: #93-031-16: "Three Month Oral (Gavage) Toxicity Study of Halofantrine Hydrochloride in Mice" have been reviewed in accordance with the Animal Care and Use Policies of the University of Illinois at Chicago. You will be pleased to know that the modifications were approved on August 23, 1994 and consequently the records of Animal Care Committee will be revised to reflect these changes.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

Sincerely yours,

Josephine B. Miller

Josephine B. Miller, Ph.D.
Chair, Animal Care Committee

JBM:st
xc: BRL

DRAFT

PROTOCOL AMENDMENT

Study No.: 166

Title: Three Month Oral (Gavage) Toxicity Study of Halofantrine Hydrochloride in Mice

1. Page 1 Section 4.0

Add the study dates as follows:

4.1	Proposed Initiation of Dosing:	02/16/95
4.2	Proposed Necropsy Dates:	05/18-19/95
4.3	Proposed Study Completion Date (Draft Study Report):	8/18/95

Reason: The study dates have been finalized.

2. Page 1 Section 5.1

Include the Walter Reed identification number, "WR171669".

Reason: Clarification of the test article used in the study.

3. Page 2 Section 5.3

Add the physical description of the test article: "White powder".

Reason: Physical description of test article was provided by the Sponsor.

4. Page 2 Section 5.4

Add the following storage conditions for maintenance of stability:

5.4.1.1	Temperature:	Room temperature
5.4.1.2	Humidity:	Ambient conditions at room temperature.
5.4.1.3	Light:	No requirements
5.4.1.4	Special Requirements:	None

Reason: Storage conditions were provided by the Sponsor.

DRAFT

PROTOCOL AMENDMENT

Study No.: 166

Title: Three Month Oral (Gavage) Toxicity Study of Halofantrine Hydrochloride in Mice

5. Page 2 Section 6.0

Change the Pathologist from "Michael J. Tomlinson, D.V.M., Ph.D., D.A.C.V.P." to "Robert L. Morrissey, D.V.M., Ph.D., D.A.C.V.P.".

Reason: Dr. Tomlinson has resigned from Pathology Associates Inc. (our pathology subcontractor).

6. Page 4 Section 8.1

Indicate the dose levels as follows:

"Low" = "1" mg/kg/day

"Mid" = "5" mg/kg/day

"High" = "25" mg/kg/day

Reason: Dose levels have been selected following consultation with the Sponsor.

7. Page 4 Section 8.2

Add the following sentence "To acclimate them to the procedure, all animals will receive vehicle by gavage for the 3 days immediately prior to the first day of dosing."

Reason: Clarification of the protocol.

8. Page 5 Section 8.6

Replace the second paragraph with the following "Each test article dosing suspension will be prepared individually by adding the appropriate amount of halofantrine with approximately one-third to one-half of the required 0.5% methylcellulose vehicle in a pre-calibrated beaker. The contents will be mixed with an Omni-Mixer homogenizer, for at least 2 minutes. The mixture will then be brought to the final volume using vehicle and again mixed for an additional 2 - 5 minutes. All suspensions will be stored at 2 - 8°C. All suspensions will be allowed to warm to room temperature and stirred continuously before and during gavage administration. Dosing suspensions prepared for use in weeks 1, 3, 7, 10 and 13 will be analyzed, and only suspensions within 10% of their target concentration will be used. Approximately 10 ml from all dosing suspensions will be reserved, frozen and retained for possible analysis."

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PROTOCOL AMENDMENT

Study No.: 166

Title: Three Month Oral (Gavage) Toxicity Study of Halofantrine Hydrochloride in Mice

8. (contd.)

Reason: The method of test article dosing suspension preparation has been changed to conform to Sponsor recommendations of mimicking the procedure used by Hazelton Washington, Inc. (2 year carcinogenicity study of halofantrine in rats).

9. Page 6 Section 8.7.7

A. Indicate that the measurement of thyroid stimulating hormone (TSH) will not be performed at UIC, but frozen serum will be sent to Anilytics Incorporated (Gaithersburg, MD) for analysis. The measurement will be performed under GLP regulations.

B. Indicate that Globulin is a calculated value.

Reason: Clarifications of the protocol.

Approvals:

STUDY DIRECTOR: _____ 2/7/95
Barry S. Levine, D.Sc. D.A.B.T. Date

SPONSOR APPROVAL: _____ 2/9/95.
George J. Schieferstein, Ph.D. Date
Contracting Officer's
Representative (COR)

DRAFT

PROTOCOL AMENDMENT

Study No.: 166

Title: Three Month Oral (Gavage) Toxicity Study of Halofantrine Hydrochloride in Mice

10. Page 3 Section 7.8

Replace the third sentence with the following: "This number will appear as an ear tag and will also be coded on a subcutaneously implanted microchip. It will also appear on a cage card visible on the front of each cage."

Reason: Clarification of the protocol. We implemented an implantable microchip identification system for use in this GLP toxicology study.

Approvals:

STUDY DIRECTOR: _____ 7/14/95
Barry S. Levine, D.Sc. D.A.B.T. Date

SPONSOR APPROVAL: _____ 10/6/95
George J. Schleferstein, Ph.D. Date
Contracting Officer's
Representative (COR)

DRAFT

APPENDIX 13

STUDY DEVIATIONS

THREE MONTH ORAL (GAVAGE) TOXICITY STUDY OF HALOFANTRINE HYDROCHLORIDE IN MICE

Study Deviations*

Deviation Type	Specific Deviation	Effect on Study
Protocol	On a few occasions, the relative humidity and/or temperature deviated outside the specified ranges in the animal room. The relative humidity and temperature deviations ranged from -13 to +0% and -2 to +2°F, respectively, outside the specified ranges.	None
Protocol	In addition to the orbital sinus, blood was collected via intracardial puncture from several animals (animal nos. 223, 224, 226, 230, 246, 247, 261, 263, 268 and 269) for clinical chemistry determinations.	None. Clinical chemistry parameters are not affected by the site of blood collection.
Protocol	A mixture of 70% CO_2:30% O_2 was used for anesthesia for blood collection instead of 80% CO_2:20% O_2.	None

*The detailed "Deviation Reports" are contained in the raw data which are archived at the Toxicology Research Laboratory, University of Illinois at Chicago, Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612.

The above deviations did not affect the integrity of the study.

Barry S. Levine, D.Sc., D.A.B.T.

Date